Novel Strategies for Synthesising and Labelling the Heteroatom-trifluoroethyl Motif

A thesis submitted to the Board of the Faculty of Mathematical, Physical and Life Sciences Division, in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Oxford



Stephen Hyde

Wolfson College

University of Oxford

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Author's Declaration

The work presented in this thesis was conducted under the supervision of Prof. Véronique Gouverneur and carried out at the Chemistry Research Laboratory, University of Oxford, unless otherwise specified. All the work is my own, except where stated otherwise, and has not been submitted for any other degree at this or any other university.

Stephen Hyde

01st September 2018

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Finally, to my family – without whom none of this would be possible.

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To John Neil Dillon, an inspirational grandfather.

Abstract

The expansion of methodologies to access fluorinated molecules is vital to the pharmaceutical and agrochemical industry. Novel protocols will complement existing routes to accessing proven useful fluorinated motifs, and for accessing new chemical space. Such fluorinated scaffolds may be [^{18}F]-radiolabelled, generating tracers which may be used to produce medical images through Positron Emission Tomography (PET). Improvement in [^{18}F]-radiolabelling techniques will simplify access to current PET tracers and allow the development of original tracers, potentially enhancing image quality or permitting images of a wider range of clinical problems.

This thesis will focus on the synthesis and labelling of the heteroatom-trifluoroethyl motif. A general introduction is presented in **chapter 1**, covering pharmaceutically relevant examples of this structural family, as well as synthetic methodology for accessing them.

Chapter 2 covers novel strategies for synthesising the heteroatom-trifluoroethyl motif by heteroatom-hydrogen bond insertion with trifluorodiazoalkanes.

Chapter 3 describes the [^{18}F]-radiolabelling of one of the sub-categories of the heteroatom-trifluoroethyl motif – the trifluoroethoxy group.

A **Conclusion** is given to summarise the scientific contribution of this body of work.

Chapter 4 provides the experimental data for compounds described in this thesis, as well as procedures for their synthesis.

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Abbreviations, Symbols and Acronyms

α	Alpha, alpha particle
β^+	Positron
γ	Gamma
δ	delta
Δ	Heat
λ	wavelength
ν	wavenumbers (cm^{-1})
χ	Pauling electronegativity
^oC	Celcius
Å	Angström (10^{-10} m)
aq	aqueous
Ar	aryl
BINAP	(2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl)
Bq	Becquerel
br	broad
c.a.	Carrier added
cal.	calories
cat.	catalytic/catalyst
CI	chemical ionisation
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
E^+	Electrophile
ee	enantiomeric excess
EI	electrospray ionization
EoB	End of bombardment
EoS	End of Synthesis
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
eV	electron Volt
FI	field ionisation
g	gram(s)
gem–	Geminal
h	hour(s)
Het	heteroatom
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	Hertz
hν	light energy
*i*Pr	isopropyl
IR	Infrared Spectroscopy
J	scalar coupling constant

K_{222}	Kryptofix 2.2.2, 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane
kcal	kilocalorie
L	ligand; litre(s)
LA	Lewis acid
LG	leaving group
M	metal; moles per cubic decimetre (mol dm^{-3})
MA	Molar Activity
Me	methyl
MeCN	acetonitrile
min	minute(s)
mol	mole(s)
Mp	melting point
MS	molecular sieves
n	number of runs
n.c.a.	No-carrier added
nm	Nanometre(s)
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	Acetate
OTf	triflate, trifluoromethanesulfonate
PET	positron emission tomography
Ph	phenyl
pin	pinacol
pKa	acid dissociation constant
ppm	parts per million
R	alkyl group
RCC	radiochemical conversion
RCY	radiochemical yield
RDS	rate-determining step
rt	room temperature
s	Second(s)
SA	Specific activity
SM	starting material
$t_{1/2}$	Half-life
TBAF	Tetrabutylammonium fluoride
*t*Bu	*Tert*-butyl
TEAF	Tetraethylammonium fluoride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilyl
t_R	Retention time, residence time
XHI	Heteroatom-hydrogen Insertion Reaction

INTRODUCTION

Chapter 1: Introduction

1.1 General Introduction

One of the primary motivators for both academic and industrial research in the pharmaceutical industry is the search for 'special effect' chemical entities – chemicals with novel properties which may be exploited to induce a desired effect in the body, and ultimately, benefit mankind. There exist many ways of creating such unique systems capable of initiating responses within the body, but fluorine substitution of organic molecules is perhaps unique in its conceptual simplicity, yet can lead to a variety of desirable features of a drug.[1]

Fluorine is the most electronegative of all elements (χ = 4.0 on the Pauling scale)[2] and has a van der Waals radius of 1.47 Å – between that of hydrogen and oxygen.[3] The same is true for the C-X bond lengths, whereby the average C-F bond is 1.35 Å long, between that of C-H and C-O.[4] Furthermore, C-F bond is the strongest covalent bond in organic chemistry (D_o = 485 kJmol^{-1}).[5-7] The strength of the bond is attributed to significant electrostatic attraction between $F^{\delta-}$ and $C^{\delta+}$ rather than the more classical electron sharing of a covalent bond (**Table 1.1**).[8,9]

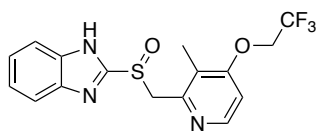
Table 1.1 Properties of hydrogen, oxygen and fluorine.[2-7]

Atom/ X	Electronegativity/ χ	van der Waals radii/ Å	C-X bond length/ Å	C-X bond strength/ kJmol^{-1}
H	2.20	1.20	1.09	411
O	3.44	1.52	1.43	358
F	4.00	1.47	1.35	485

Due to the minimal steric disruption imparted to the molecule, hydrogen may be replaced with fluorine. However, such a replacement has significant electronic consequences and can dramatically change the properties of a drug molecule, including:

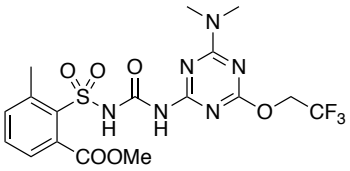
conformational changes; changes in reactivity; reduction of pK_a; modulation of lipophilicity; and increased metabolic stability – resulting in knock-on effects, such as increased potency and reduced toxicity.[4,10] Oxygen may also be replaced by fluorine – a much less dramatic change in that one electronegative atom replaces another. However, replacement of C=O with CFH or CF_2 involves a hybridisation change, introducing an additional level of complexity in the form of a stereogenic carbon in the case of CHF.[11]

This potential for drastically improving the profile of a drug is often the driver for such strategic fluorination in medicinal chemistry, and has initiated a rapid expansion in methods to introduce fluorine and fluorinated groups into a molecule.[12] Due to the aforementioned properties that fluorine can impart to a drug molecule, it is estimated that fluorine is found in 20-25 % of drugs in the pharmaceutical pipeline and 30 % of agrochemicals.[13,14] One family of fluorinated functional groups identified by our industrial collaborators – AstraZeneca – as underexplored in terms of general synthetic methodology, is the heteroatom-trifluoroethyl motif (X-CH(R)CF_3, where X is a heteroatom). The presence of this structural motif in already-existing market drugs is highlighted in **Figure 1.1**.



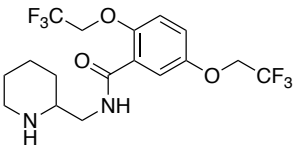
Takepron (Lansoprazole)
gastric acid secretion regulator





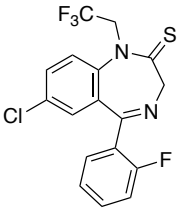
Triflusulfuron (Debut)
herbicide





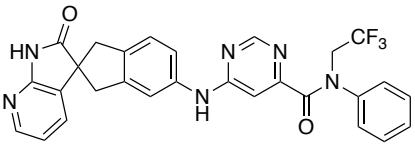
Flecainide (Tambocor)
antiarrhythmic agent





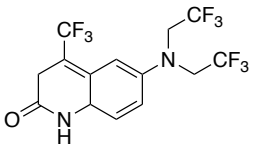
Quazepam (Doral)
treats insomnia





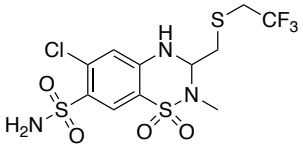
GWM2
CGRP-antagonist





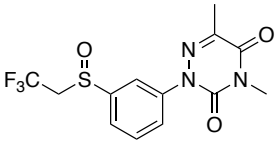
LGD2226
androgen receptor modulator





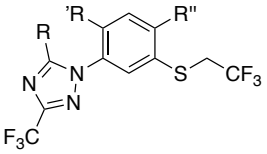
Polythiazide (Renese)
diuretic





US2016251321
pesticide





US2013046002
pesticide



Figure 1.1 Bioactive molecules containing the heteroatom-trifluoroethyl motif.[15-21]

1.2. Trifluoroethyl Ethers

1.2.1 Trifluoroethyl Aryl Ethers

The aryl-trifluoroethoxy group displays increased resistance to metabolism by cytochrome P450, one of the body's primary enzymes for drug metabolism.[22] In the development of Silodosin (**Figure 1.2**), a drug used for the treatment of benign prostate hyperplasia, an increase in selectivity for the human tissue (liver and prostate) α_{1a}-androgen receptors was observed upon replacing the ethoxy group with the trifluoroethoxy counterpart.[23,24]

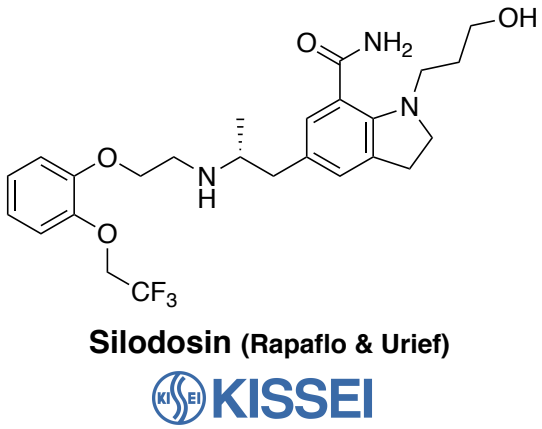


Figure 1.2 Silodosin contains the aryl-trifluoroethoxy group–critical for its increased selectivity.[23,24]

Furthermore, the trifluoroethoxy group has been added to aryl rings to enhance the lipophilicity of phthalocyanine-based drug carriers,[25] and even explored as a novel phenol protecting group due to its ability to survive harsh oxidative and reductive cleavage conditions.[26-28]

Methods of accessing the aryl-trifluoroethoxy group are varied, with multiple disconnections possible (**Figure 1.3**):[27,29] the use of phenols in substitution reactions

with trifluoroethyl electrophiles (**A**);[30,31] the utilisation aryl halides as starting materials, which undergo S_NAr reactions,[32] Buchwald-Hartwig etherifications,[33,34] and Ullmann-type copper-catalysed coupling reactions (**B**).[35,36] This same disconnection is also feasible through Chan-Evans-Lam oxidative cross couplings (X = $B(OH)_2$/BF_3K).[37,38] More contemporary methods for accessing this motif employ transition-metal-catalysed direct C-H bond functionalization, an approach that has seen much interest since Sanford's pioneering work of palladium-catalysed directed C-H alkoxylation of arenes with $PhI(OAc)_2$ as the terminal oxidant (**C**).[29,39-44] Other, less obvious means of accessing the trifluoroethoxy group include: the acid-catalysed reaction of phenols with trifluorodiazoethane (**D**);[45] Umemoto's use of trifluoroethyl-hypervalent iodine reagents (**E**);[46] and Ritter's PhenoFluor-mediated reaction of phenols with trifluoroethanol (**F**).[47]

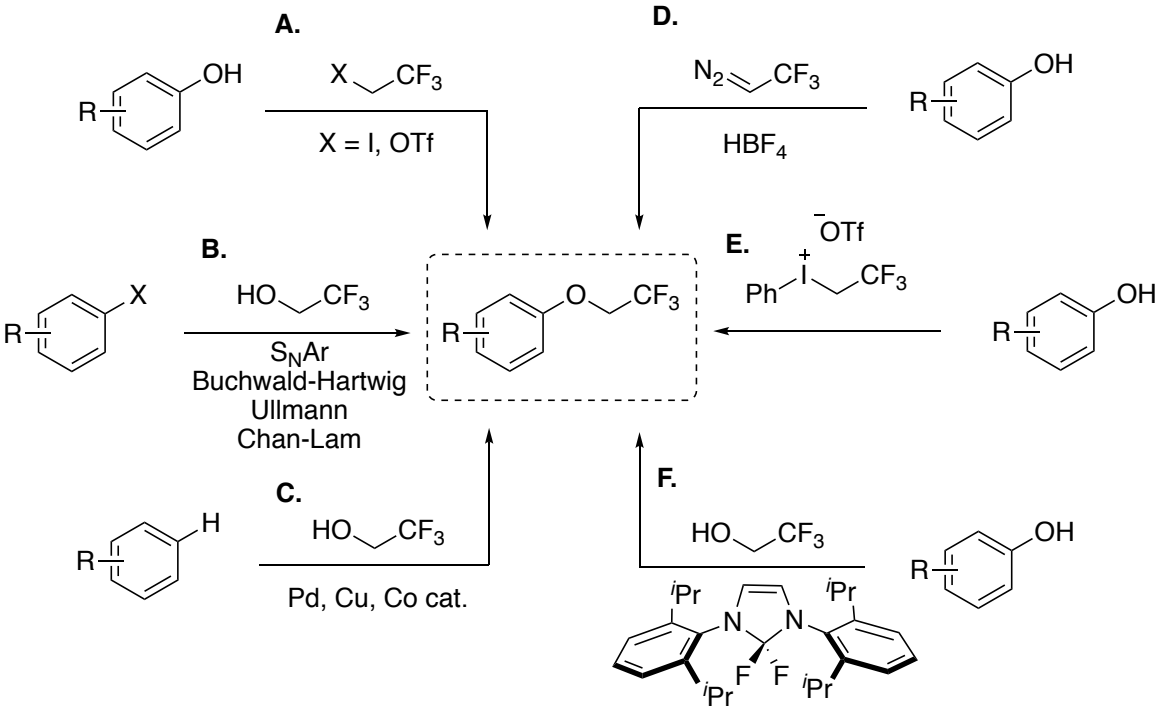


Figure 1.3 Methods of introducing the aryl-trifluoroethoxy group.

1.2.2 α-Substituted Trifluoroethyl Aryl Ethers

α-Branched trifluoroethoxy groups are less common although still represented in biologically active molecules (**Figure 1.4**).

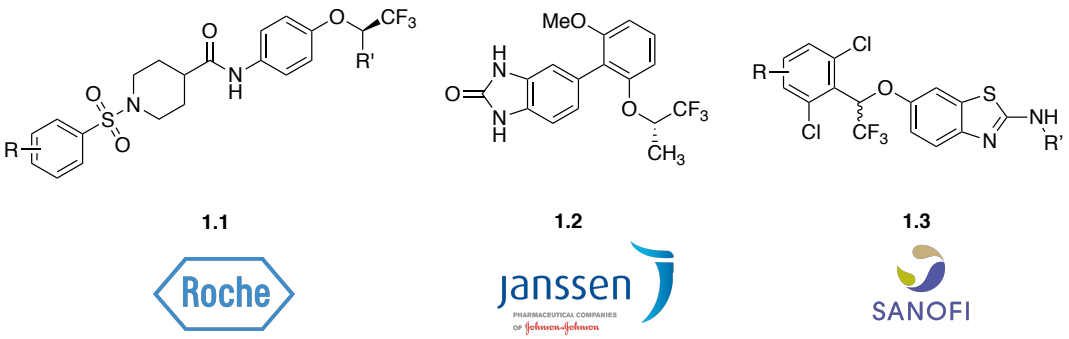


Figure 1.4 Bioactive molecules containing the α-branched trifluoroethoxy group.[48-50]

Several strategies have been reported for the synthesis of α-branched trifluoroethoxy scaffolds (**Figure 1.5**): S_NAr reactions between aryl halides and the corresponding α-branched-2,2,2-trifluoroethanol,[51,52] or direct displacement of the nitro group (**A**);[53] Williamson-type substitution reactions (**B**);[54-56] Mitsunobu-type reactions (**C**);[57,58] and carbene insertion into the O-H bond of phenols (**D**).[59,60] Enantiopure α-branched trifluoroethoxy compounds are obtained either by substitution with enantiopure α-branched-2,2,2-trifluoroethanol starting materials or by chiral resolution techniques.[48-50]

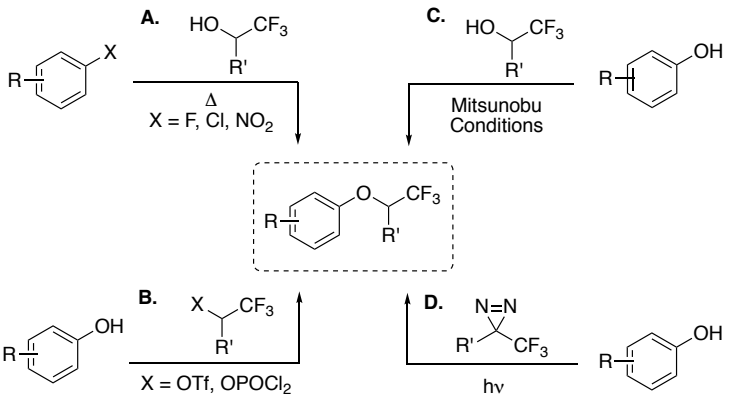


Figure 1.5 Strategies for synthesis of the α-branched trifluoroethoxy group

1.2.3 Trifluoroethyl Alkyl Ethers

Non-phenolic trifluoroethoxy molecules also have great synthetic importance – low molecular weight fluorinated ethers are widely used as anaesthetics, such as Isoflurane, Desflurane, Sevoflurane, and Fluroxene (**Figure 1.6**).[61,62]

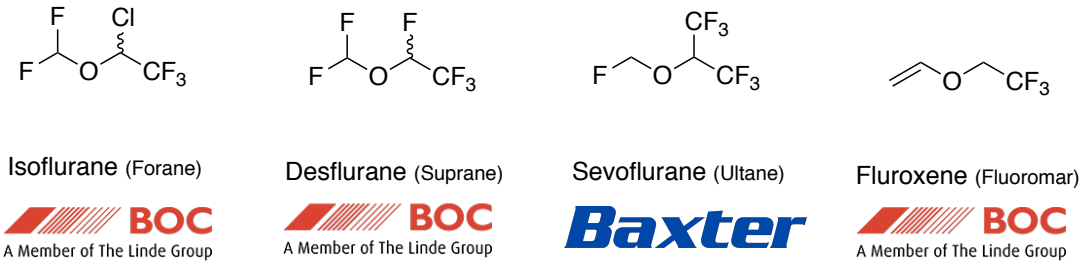


Figure 1.6 Anaesthetics bearing the trifluoroethoxy group.[61,62]

Alkyl-trifluoroethoxy ethers may be synthesised *via* a wide range of methods (**Figure 1.7**). Industrially these molecules are made by direct fluorination of simple alkyl ethers or chlorinated ethers with fluorine gas (**A**).[63,64] More research and development compatible routes include: substitution of 2,2,2-trifluoroethyl halides with alcohols in basic media (**B**);[65] substitution of alkyl halides/pseudohalides with 2,2,2-trifluoroethanol (**C**).[28,66-73] Insertion reactions of 2,2,2-trifluorodiazoethane into the O-H bond of alcohols (**D**),[45,74-77] and diazomethane into the O-H bond of 2,2,2-trifluoroethanol (**E**) are possible.[68] Mitsunobu-type reactions lend themselves to accessing this motif (**F**).[26,27,78] Nucleophilic addition of 2,2,2-trifluoroethanol to unactivated alkenes is also a reliable method (**G**).[79,80] More atypical methods for trifluoroethylating alcohols include: use of Umemoto's hypervalent iodine reagent (**H**);[81] the use of bis(2,2,2-trifluoroethoxy)triphenylphosphorane (**I**);[82,83] and the triazine derived reagent 2,4,6-tris-(2,2,2-trifluoro-ethoxy)-[1,3,5] triazene (TriTFET) (**J**).[84]

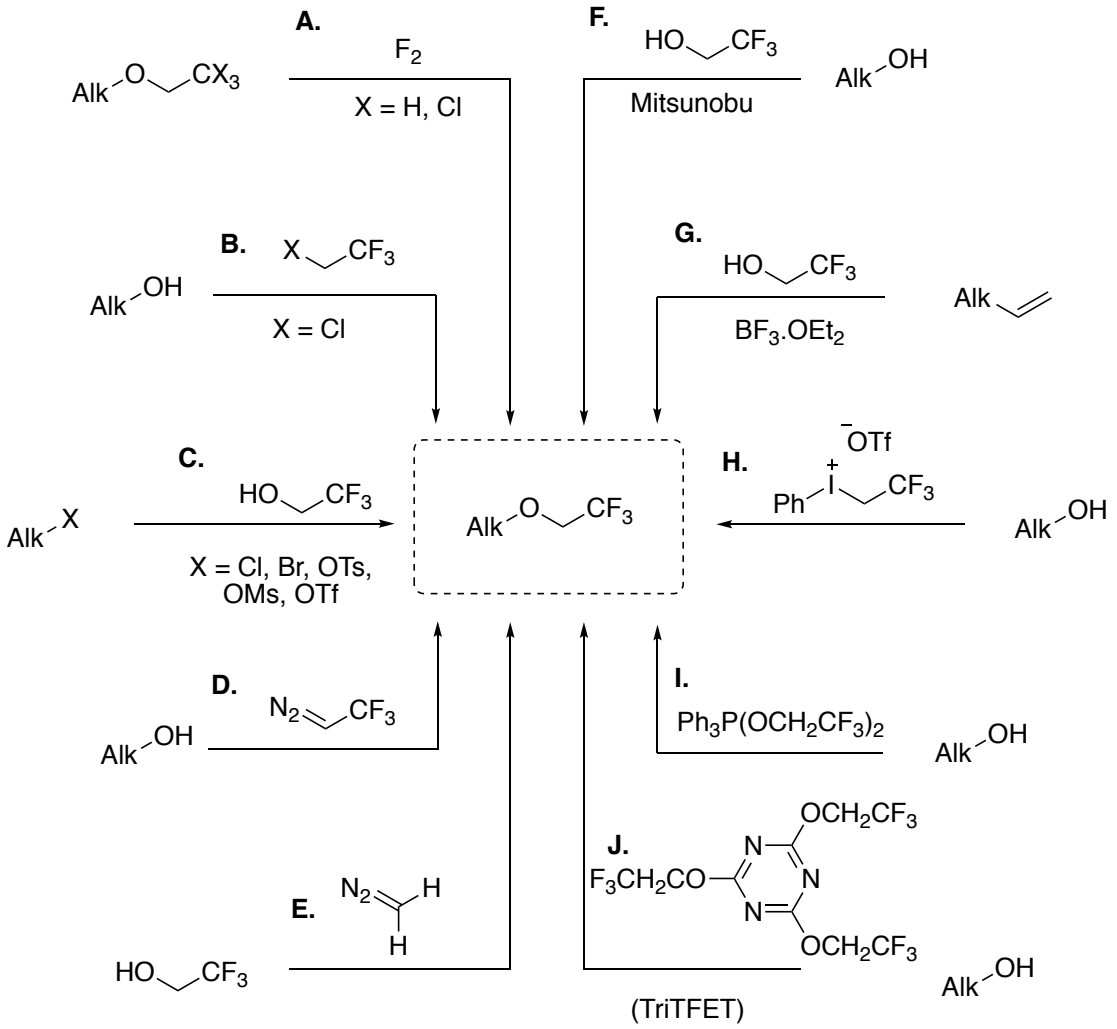
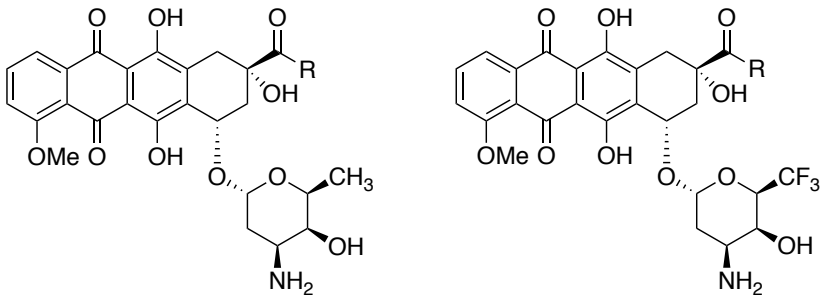


Figure 1.7 Methods for accessing the alkyl-trifluoroethoxy group.

Much attention has been given to the synthesis of α-trifluoromethyl oxygenated heterocycles, especially to those based on tetrahydropyran.[85] This has resulted in a multitude of α-trifluoromethylated carbohydrate mimetics,[86,87] some of which have demonstrated powerful antitumor activity, such as **1.6** and **1.7** – fluorinated analogues of the chemotherapy drugs Daunorubicin (Cerubidine, Sanofi-Aventis **1.4**) and Doxorubicin (Adriamycin, Pfizer **1.5**).(**Figure 1.8**).[88-90] Here, a CF_3 group has replaced the CH_3 group typical of anthracycline antibiotics at the C5' position. This replacement stabilises the glycosidic bond against acidic hydrolysis by decreasing the electron density at the glycosidic oxygen, and thus restricting protonation. When these fluorinated

analogues were tested against L1210 murine leukemia *in vivo* they exhibited increased antitumor activity compared to both Daunorubicin and Doxorubicin. This is thought to originate from the higher lipophilicity of the CF_3 group, compared with the CH_3 group, enhancing the cellular uptake and facilitating the transportation of the compound into organs.



1.4 R = H (Daunorubicin, Sanofi-Aventis)
1.5 R = CH_2OH (Doxorubicin, Pfizer)

1.6 R = H
1.7 R = CH_2OH

Figure 1.8 Fluorinated analogues of the chemotherapy drugs Daunorubicin (Cerubidine) and Doxorubicin (Adriamycin).[88-90]

These non-phenolic α-substituted trifluoroethoxy compounds are generally synthesised from alkyl halides, by substitution reaction with the alkoxide anion formed from deprotonation of secondary α-trifluoromethyl alcohols (themselves formed from trifluoromethyl attack of ketones or by nucleophilic attack of an α-trifluoromethyl ketone) (**Figure 1.9**).[67,91-93]

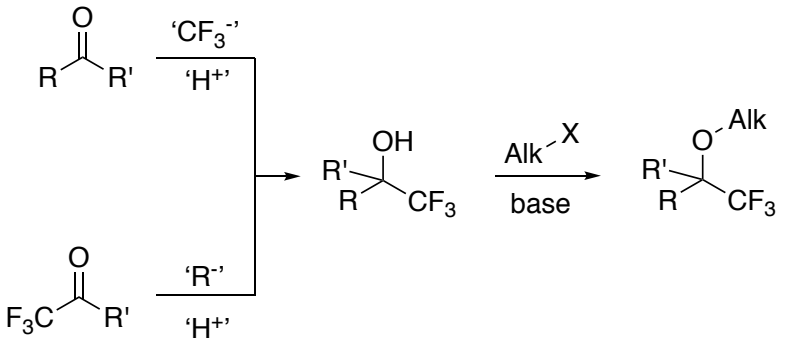


Figure 1.9 General synthesis of non-phenolic α-substituted trifluoroethoxy compounds.[67,91-93]

A famous example of this synthetic route is Efavirenz (Sustiva, Bristol-Myers Squibb) (**Figure 1.10**) – an antiretroviral medication used to treat and prevent HIV/AIDS which is on the World Health Organization's List of Essential Medicines.[94,95]

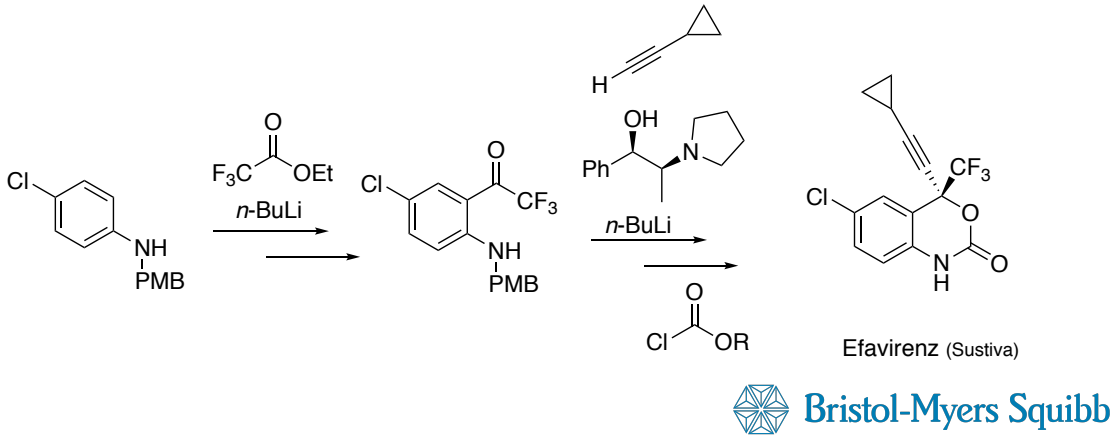


Figure 1.10 Synthesis of Efavirenz (Sustiva).[94,95]

Efavirenz is made asymmetrically in 7 steps from 4-chloroaniline. The trifluoroethoxy unit is added early in the synthesis by directed *ortho*-metalation, and the resulting anion quenched with ethyl trifluoroacetate. Enantioselective addition of the Li-acetylide to the ketone is achieved with the addition of a chiral Li-alkoxide mediator. After PMB deprotection, the γ-amino alcohol reacts with phosgene/chloroformate to form the chiral benzoxazinone.[95]

1.2.4 Trifluoroethyl Ethers as Synthetic Intermediates

Due to the electron donating (mesomerism) and electron withdrawing (inductive) properties of methoxytrifluoromethylcarbene **1.9**, it has been used for cyclopropanation reactions with olefins (**Figure 1.11**).[96] These 'push-pull' carbenes, generated by irradiation of methoxytrifluoromethyldiazirine **1.8**, were thought to offer enhanced stability over its non-fluorinated counterpart, methoxymethylcarbene. However, the CF_3

'pull' outweighs the MeO 'push' resulting in enhanced reactivity (reduced stability), with cyclopropanation occurring rapidly and at a similar rate, regardless of the electronic demands of the alkene.

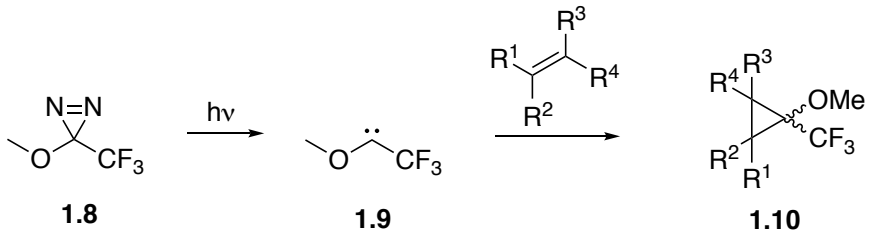


Figure 1.11 'Push-pull' carbenes of the 2,2,2-trifluoroethoxy group.

α-Branched trifluoroethoxy groups have found application as synthetic intermediates, for example, in the synthesis of terminal vinyl monofluorides **1.13** *via* Suzuki-Miyaura coupling, with 2,2,2-trifluoro-1-phenyl tosylates **1.11** acting as precursors for the required pseudohalide coupling partners.[97]

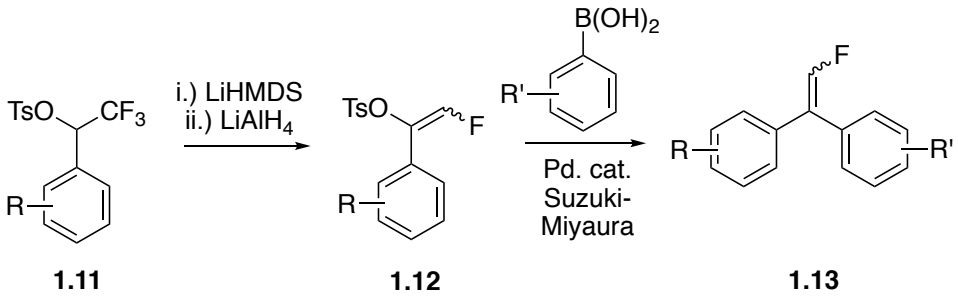


Figure 1.12 Synthesis of terminal vinyl monofluorides *via* Suzuki-Miyaura coupling.[97]

Tredwell and co-workers successfully used α-(trifluoromethyl)benzyl tosylates **1.14** directly as coupling partners in Suzuki-Miyaura reactions to generate 1,1-diaryl-2,2,2-trifluoroethanes **1.16**.[98] This disconnection is not trivial, since trifluoromethyl groups bound geminal to transition metals are susceptible to non-desirable β-fluoride elimination;[99,100] the use of the XPhos-Pd-G2

precatalyst – developed by Buchwald and co-workers – proved crucial to overcoming this unwanted side reaction.[101]

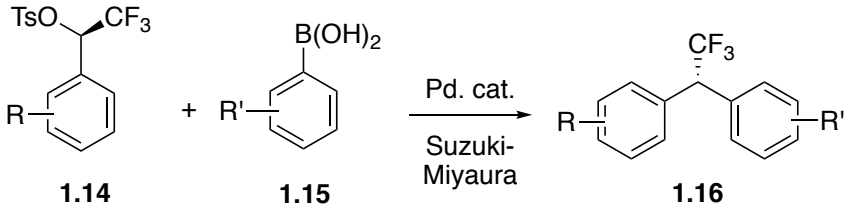


Figure 1.13 Suzuki-Miyaura coupling of α-(trifluoromethyl)benzyl tosylates with aryl boronic acids.[102]

α-Hydroxy trifluoroethyl ethers **1.17** also serve as reliable electrophiles in the presence of acid catalysts (**Figure 1.14**), such as: Friedel-Crafts-type reactions with arenes to generate 1,1-diaryl-2,2,2-trifluoroethanes **1.18**;[103-105] or in the formation of *N,O*-hemiacetal intermediates **1.19**.[106]

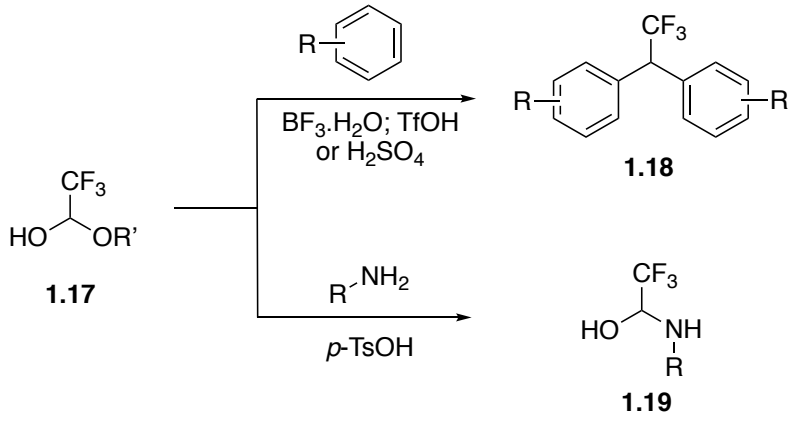


Figure 1.14 α-Hydroxy trifluoroethyl ethers acting as electrophiles.[103-105]

1.3 Trifluoroethylamines

1.3.1 Aryl-trifluoroethylamines

N-Fluoroalkylation can have a profound impact on the physiochemical properties of drug candidates,[107,108] with the trifluoroethylamine moiety being a well-represented structural group within this family.[109-112] It has been incorporated into the structure of benzodiazepines to enhance their pharmacological properties; as in the case of Diazepam (Valium, Hoffmann-La Roche) (**Figure 1.17**) – a medication used for the treatment of multiple symptoms including anxiety and insomnia. Metabolic studies of diazepam showed that the principal phase I reaction is dealkylation followed by further oxidation to yield a range of metabolites that exhibited neurotoxicity.[113,114] *N*-trifluoroethylation was used to resist this dealkylation and resulted in the generation of Halazepam (Merck & Co.)[115]– a drug with comparable anti-anxiety properties but significantly reduced neurotoxicity.[116] In fact this discovery spawned a small family of *N*-trifluoroethylated benzodiazepine analogues (**Figure 1.17**).[117]

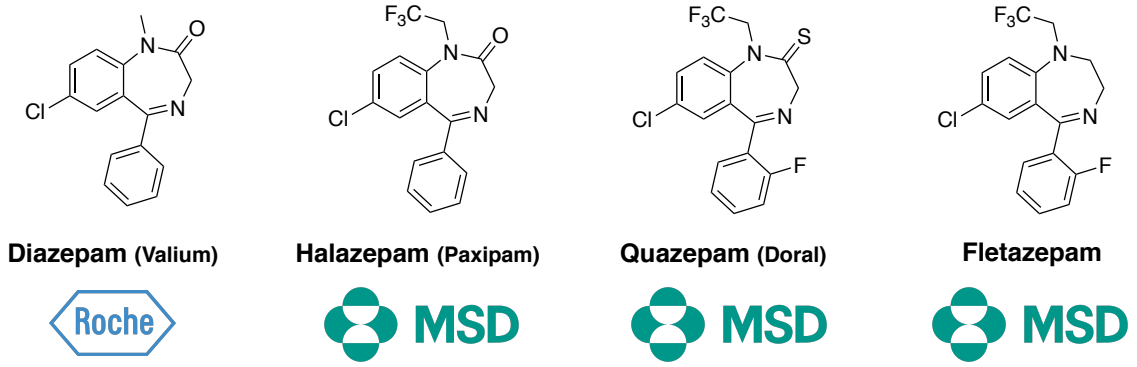
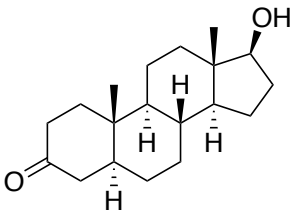


Figure 1.17 Family of *N*-trifluoroethylated benzodiazepines.

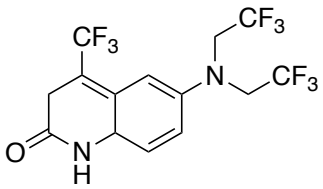
Bis-*N*-trifluoroethylated anilines **1.21** have been identified as orally available, tissue-selective androgen receptor modulators for the treatment of low testosterone levels (**figure 1.18**).[118,119] The trifluoroethyl groups are crucial to the mode of action of

this drug, with the fluorinated analogue being greater than 10-fold more potent than the corresponding ethyl variant; cocrystal structures of **1.21** in the hAR ligand binding domain show that it occupies the same binding pocket as dihydrotestosterone (DHT) **1.20**, with the two trifluoroethyl groups occupying the same space in the receptor as the C and D rings of the steroid.[17]



1.20

DHT



1.21

LGD2226

Ligand

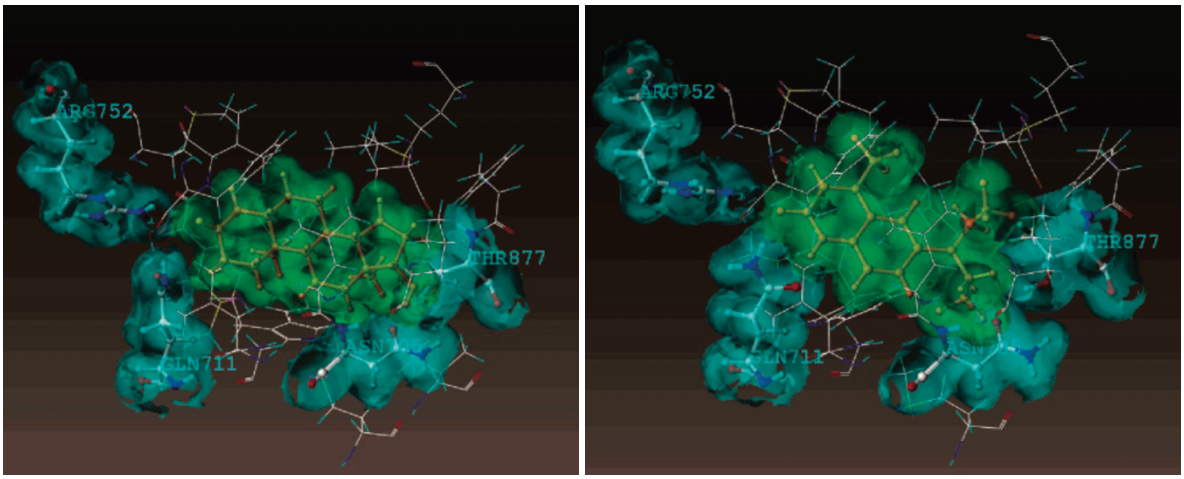


Figure 1.18 LGD2226 binds to the same receptor as DHT.[17] Reprinted with permission from American Chemical Society. Copyright 2012. PDB reference: AR LBD–LGD2226, 2hvc, r2hvcsf.

N-Trifluoroethylated anilines have found applications in the dye industry; a direct consequence of the unique electronic properties of this fluorinated unit, which allow fine colour tuning of azo dyes.[120] Due to the chemical robustness of the trifluoroethylamine group, this has the serendipitous advantage of increasing its 'gas- and lightfastness' – a measure of a dye's resistance to fading when exposed to the atmosphere and light.[121]

Methods for accessing this group have evolved considerably over the past half-century (**Figure 1.19**); initial processes utilised anilines and fluoroalkyl halides/pseudohalides, although these reactions were performed in an autoclave and exhibited limited functional group tolerance (**A**).[116,121] Reductive amination is a widely used method for accessing alkylated amines, including *N*-trifluoroethylated anilines (**B**);[122,123] as is reduction of trifluoroacetamides (**C**).[124-127] S_NAr reactions are possible but only with highly activated alkyl halide substrates at high temperatures in a sealed vessel (**D**).[128] Aryl halides have also been used for palladium-catalysed arylations of trifluoroethylamine by Hartwig,[129] and nickel-catalysed aryl aminations by MacMillan (**D**).[130] Other methods include: Umemoto's trifluoroethylation of anilines using trifluoroethyl-hypervalent iodine (**E**);[46] silver-catalysed insertion of trifluorodiazoethane into the N-H bond of anilines (**F**);[131] and a recent novel strategy employing trifluoroethanol activated by 2,4,6-trichloro-1,3,5-triazine (TCT) (**G**).[132]

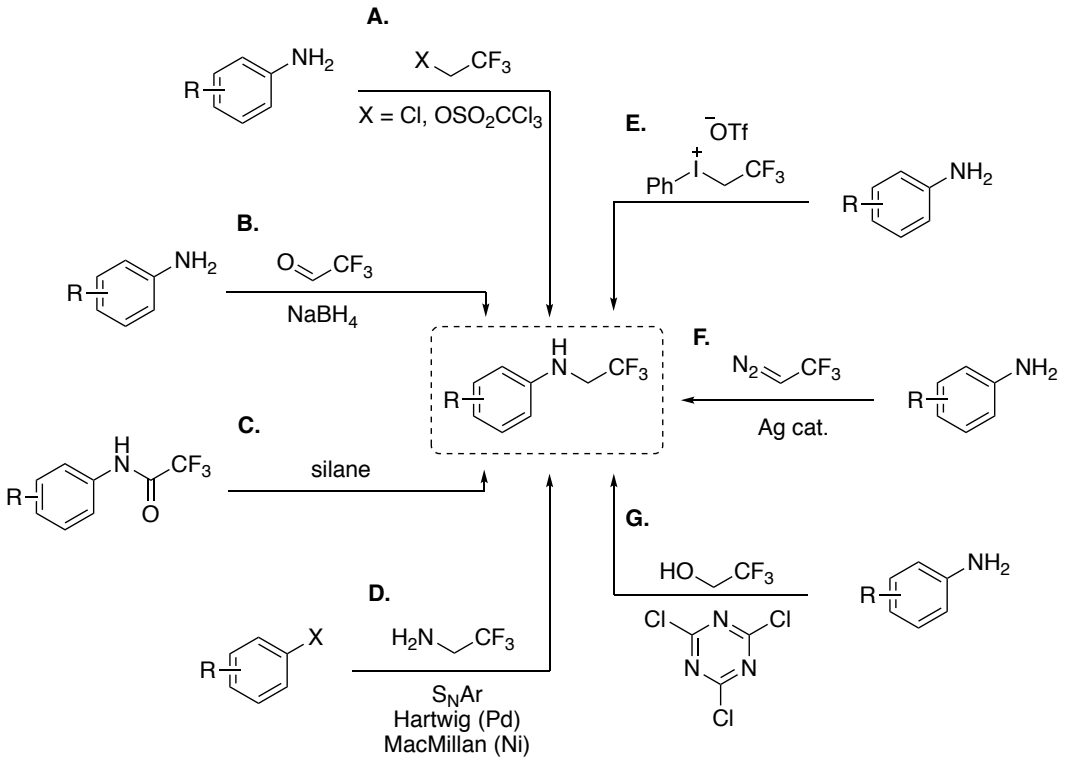
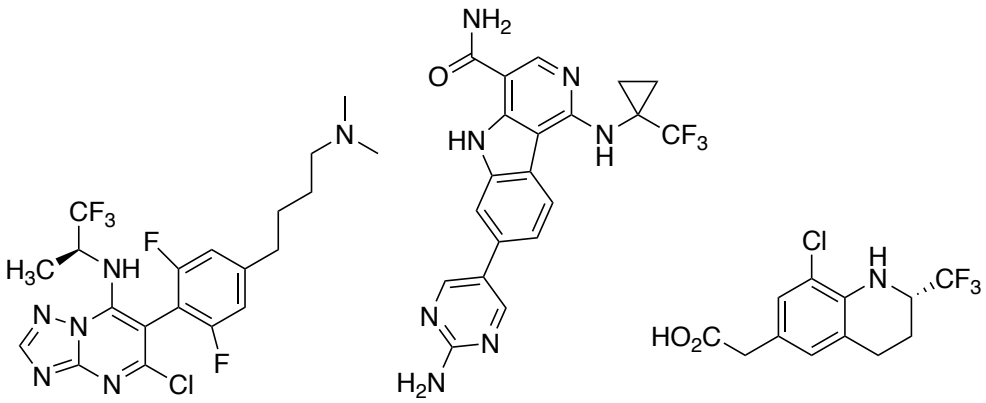


Figure 1.19 Methods of introducing the trifluoroethylamine group.

1.3.2 α-Substituted Aryl-trifluoroethylamines

α-Substituted trifluoroethylamino compounds are also well represented in the pharmaceutical pipeline (**Figure 1.23)**. For example, in the development of the anticancer drug **1.22**, Beyer and co-workers found the 2,2,2-trifluoro-1-methylethylamino group essential for achieving high potency.[133] In the evolution of **1.23**, a drug used to treat myeloproliferative disorders, Merck & Co. successfully introduced the α-branched trifluoroethylamine group to resist oxidative metabolism of the amino group at the 1-position – a pathway that had been determined as the major cause of drug clearance.[134] Furthermore, whilst developing the disease-modifying antirheumatic drug (DMARD) drug, **1.24**, for the treatment of rheumatoid arthritis, Kyorin Pharmaceuticals found the α-branched trifluoroethylamine moiety to be significantly better at antibody inhibition than the corresponding, non-fluorinated, α-branched ethylamine analogue.[135]



1.22 **1.23** **1.24**

Figure 1.23 Bioactive molecules containing the α-substituted trifluoroethylamino group.

The α-substituted trifluoroethylamino group may be accessed *via* a variety of methods (**Figure 1.21**).

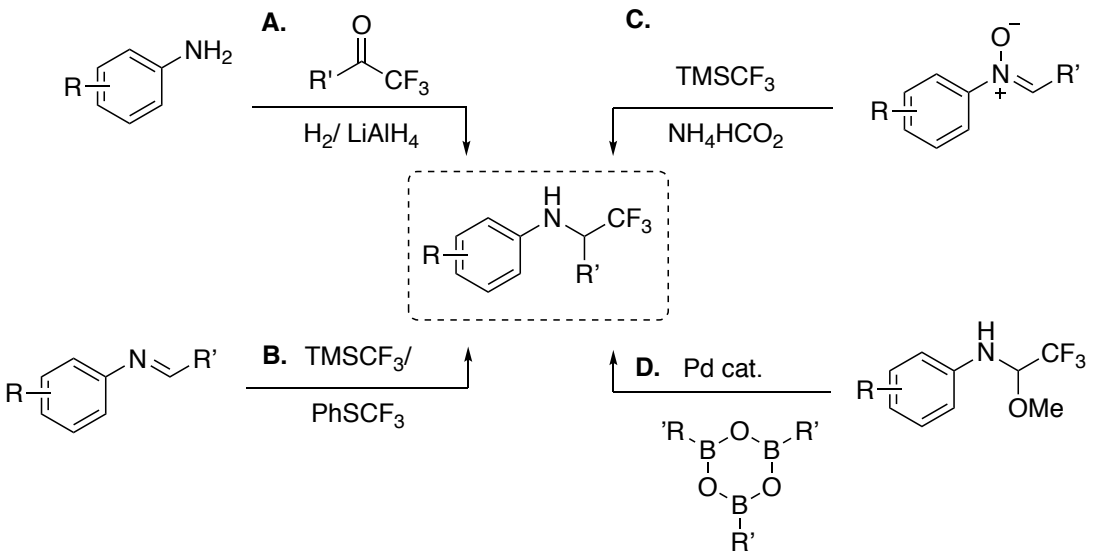
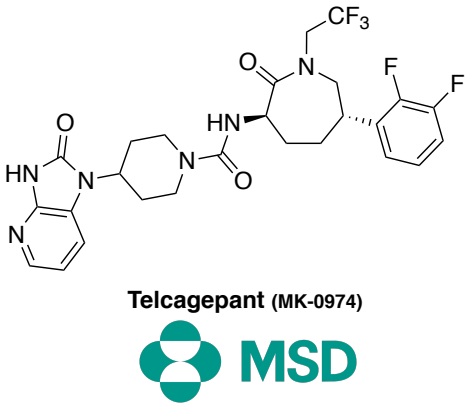


Figure 1.21 Methods for preparing the α-substituted trifluoroethylamino group.

Reductive amination of the ketimine formed by condensation of anilines with α-trifluoromethyl ketones reliably generates this structure (**A**).[136,137] Prakash popularised a method for adding the trifluoromethyl group to aldimines using Ruppert's reagent (**B**).[138-142] Earlier methods of implementing this strategy make use of ((trifluoromethyl)thio)benzene as a nucleophilic trifluoromethyl source, activated by the germyl anion (Et_3GeNa).[143,144] Preparation of α-substituted trifluoroethylamino derivatives have also been accomplished by nucleophilic trifluoromethylation of nitrones (**C**),[145] and the 1,2-nucleophilic addition of arylboroxines to *N,O*-acetals under palladium catalysis (**D**).[146,147]

1.3.3 Alkyl-Trifluoroethylamines

Non-anilinic amines containing the trifluoroethyl group are also present in many bioactive molecules, and include tertiary, secondary, and primary trifluoroethylamines in both unsubstituted and α-substituted form. In the modification of Telcagepant (Merck & Co.) (**Figure 1.20**) – a CGRP receptor antagonist for the treatment of migraine – replacing the N1 ethyl group with a trifluoroethyl group resulted in a 26-fold increase in potency.[148-150]



Telcagepant (MK-0974)

MSD

Figure 1.20 Telcagepant is an example of a tertiary non-anilinic amine containing the trifluoroethyl group.[148-150]

In the creation of second generation taxoid anticancer drugs **1.25**, Bernacki and co-workers explored α-trifluoromethylated amide analogues of the market leaders Taxol (Paclitaxel, Bristol-Myers Squibb) and Taxotere (Docetaxel, Sanofi-Aventis). These fluoro-analogues were evaluated against several human cancer cell lines: 121 (ovarian carcinoma); A549 (non-small cell lung carcinoma); HT-29 (colon carcinoma); MCF-7 (mammary carcinoma); and MCF7-R (mammary carcinoma). In virtually every case, these new taxoids were substantially more active than either Paclitaxel or Docetaxel; most notably against breast cancer cell line, MCF7-R, whereby **1.25** was one order of magnitude better.[151,152]

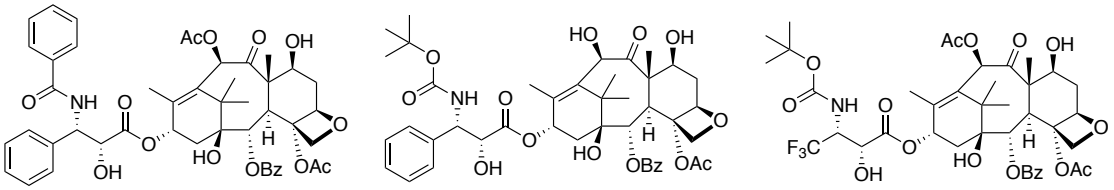
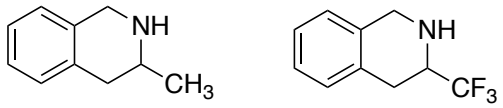


Figure 1.21 Pharmaceutically relevant examples of a secondary non-anilinic amines containing the trifluoroethyl group.

Similarly, in the evolution of the family of antihypertensive drugs **1.26b**, Grunewald and co-workers found the presence of an α-branched trifluoroethylamine group essential for drastically increasing selectivity for α_2-adrenoceptors verses the non-fluorinated variant **126a**. This is thought to result from increased penetration of the blood-brain barrier due to increased lipophilicity (**Figure 1.22**).[153]

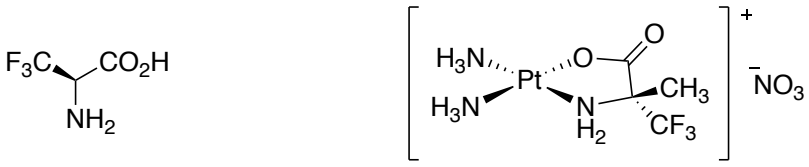


	1.26a	**1.26b**
selectivity α_2:	0.36	27

Figure 1.22 Enhanced selectivity due to the presence of the trifluoroethylamine group.

Additionally, α-trifluoromethylation of amino acids may enhance their drug-like properties.[154] Incorporation of α-trifluoromethylated amino acids into peptides can retard proteolytic degradation,[155] and enhance *in vivo* absorption and drug permeability through certain body barriers.[156] For example, 2,2,2-trifluoroalanine **1.27** has been shown as a potent enzyme inhibitor, effectively inhibiting γ-cystathionase and alanine racemase.[157] Furthermore, α-trifluoromethyl alanine (α-Tfm-Ala) **1.28** has been used as

a *N,O*-chelating ligand to platinum complexes in the development of novel antitumor drugs that exhibit activity comparable to that of cisplatin.[158]



1.27
(R)-2,2,2-trifluoroalanine

1.28
$[Pt(NH_3)_2((R)$-α-Tfm-Ala)]

Figure 1.23 Pharmaceutically relevant examples of a primary non-anilinic amines containing the trifluoroethyl group.

Non-anilinic trifluoroethylamine groups may be accessed *via* a variety of pathways (**Figure 1.24**).

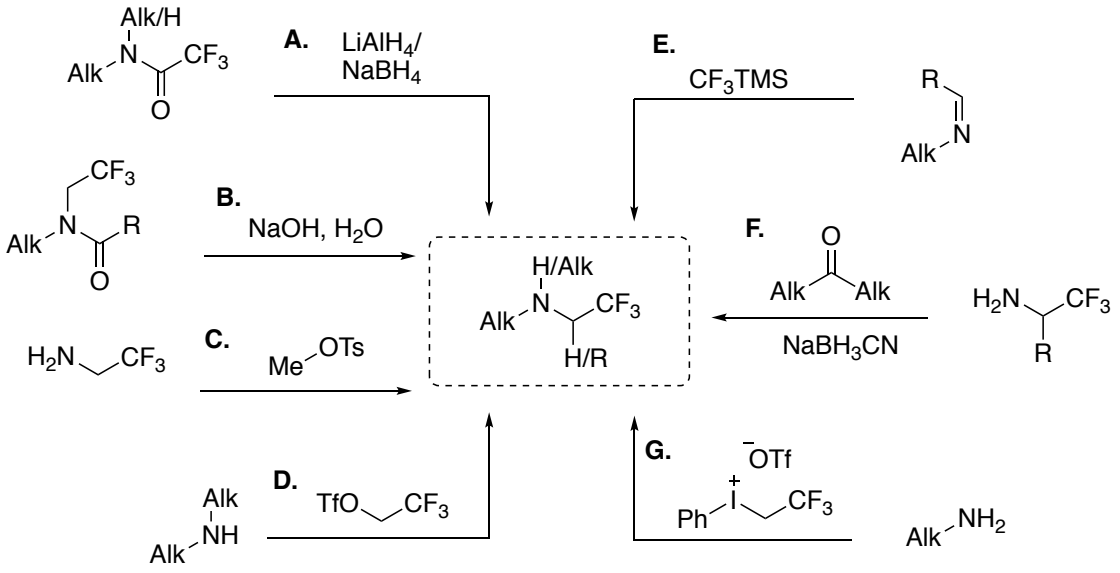


Figure 1.24 Methods of accessing non-anilinic trifluoroethylamine compounds.

Methods include: reduction of trifluoroacetamides (**A**);[159] basic hydrolysis of *N*-trifluoroethylated amides (**B**);[160] alkylation of trifluoroethylamine (**C**);[161] *N*-trifluoroethylation of amines (**D**);[162] trifluoromethylation of imines (**E**);[163] reductive amination (**F**);[164] and the use of Umemoto's hypervalent iodine reagent (**G**).[81]

1.3.4 Asymmetric Trifluoroethylamines

Asymmetric synthesis of trifluoromethylated amines is possible *via* variety of methods (**Figure 1.25**): metal-catalysed hydrogenation of α-trifluoromethyl imines utilising BINAP-derived ligands (**A**);[137,165] organocatalysed transfer hydrogenation with benzothiazolines acting as hydride donor in the presence of catalytic chiral phosphoric acids (**B**);[166] nucleophilic addition to α-trifluoromethyl imines (**C**);[167-175] trifluoromethylation of iminium ions with cinchona alkaloid catalysts (**D**);[176] and by catalytic isomerisation of imines, catalysed by dihydroquinine-based catalysts (**E**).[177]

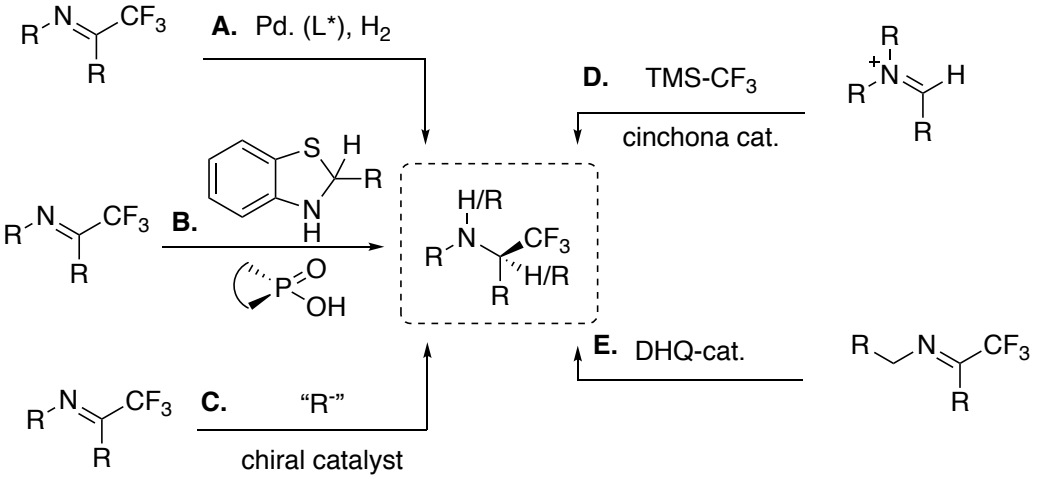


Figure 1.25 Methods of asymmetrically accessing the α-substituted trifluoroethylamino group.

1.3.5 Trifluoroethylamines as Isosteres for Amides

α-Substituted trifluoroethylamino compounds may be used as bioisosteres for the amide group.[178,179] The fundamental basis for mimicry between the $CF_3CH(R)NH$ moiety and an amide relies upon both geometrical and electronic considerations.[180] The electron withdrawing effects of the CF_3 moiety reduce the basicity of the amine such that the H-bond donating properties of the N-H are similar to that of an amide N-H.[181,182] In addition, the C-F dipoles and electron density are believed to provide some emulation of

the amide oxygen lone pairs of electrons. These structural alterations relieve topographical constraints imposed by an amide functionality which may enhance complementarity with a specific target and/or eliminate metabolic sensitivity to amidases, esterases, and proteases. However, these motifs introduce an additional level of complexity in the form of a new stereocentre. This technique has been explored in the generation of fluorinated mimetics of Thalidomide (**Figure 1.26**).[183]

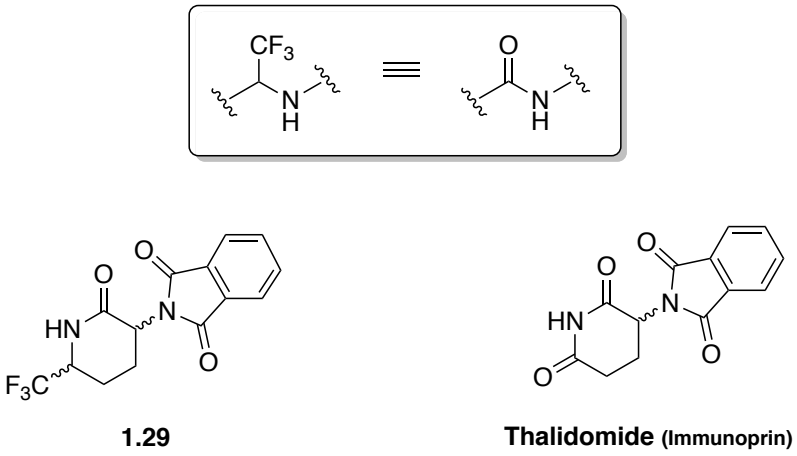
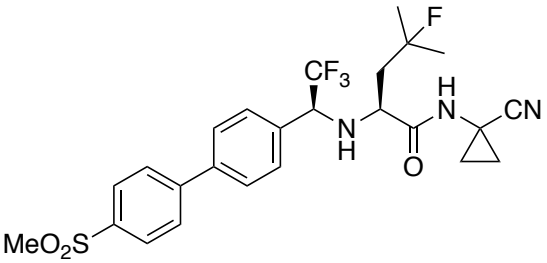


Figure 1.26 The trifluoroethylamine group as an isostere for the amide group, as exemplified by fluoro-analogues of Thalidomide.

The most prominent example of the α-substituted trifluoroethylamino group being used as a bioisostere for the amide group is in the case of the cathepsin K inhibitor Odanacatib (Merck & Co.) (**Figure 1.27**) – a mechanism-based inhibitor of the cathepsin family of cysteine protease inhibitors.[184-186] The compiled SARs indicate the importance of the trifluoromethyl functionality on the amine pK_a, as the CH_3 analogue is 1000-fold less potent. Although Odanacatib completed advanced clinical trials as a potential treatment for osteoporosis and bone metastasis – exhibiting increasing bone mineral density and reducing the risk of fractures in patients – the compound was abandoned due to the observation of an increased risk for cardiovascular events associated with drug therapy.[187]



Odanacatib (MK-0822)

MSD

Figure 1.27 The α-substituted trifluoroethylamino group as an isostere for the amide group.[184-186]

1.3.6 Trifluoroethylamines as Synthetic Intermediates

The presence of a trifluoromethyl group can drastically effect the regioselectivity of a reaction.[188] This is observed in the anodic methoxylation of *N*-methyl-*N*-(2,2,2-trifluoroethyl)aniline **1.32**, whereby the methoxy group was exclusively introduced into the α-position of the trifluoromethyl group to yield the α-methoxy trifluoroethylamino product **1.33** (**B**). This contrasts with methoxylation occurring exclusively on the methyl group of *N*-ethyl-*N*-methyl aniline **1.30** to yield the primary ether **1.31** (**A**).[189] This is rationalised as a result of the ease of removal of the proton α- to the CF_3 group relative to the CH_3 group (**Figure 1.28**).

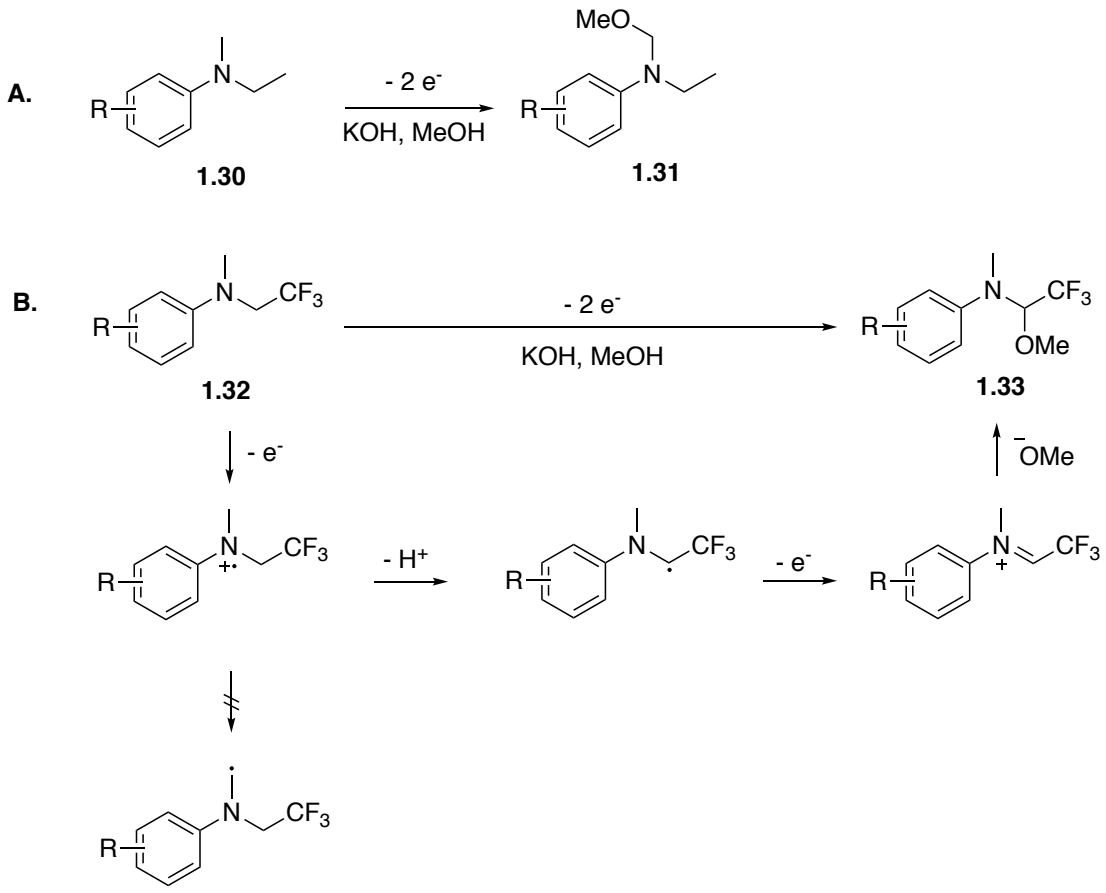


Figure 1.28 Altered reactivity of the trifluoroethylamine group.

The resulting α-methoxy trifluoroethylamino compounds **1.34** may be treated with Lewis acid to generate α-trifluoromethylated iminium cations **1.35**, which may be trapped with various nucleophiles (**Figure 1.29**).[189]

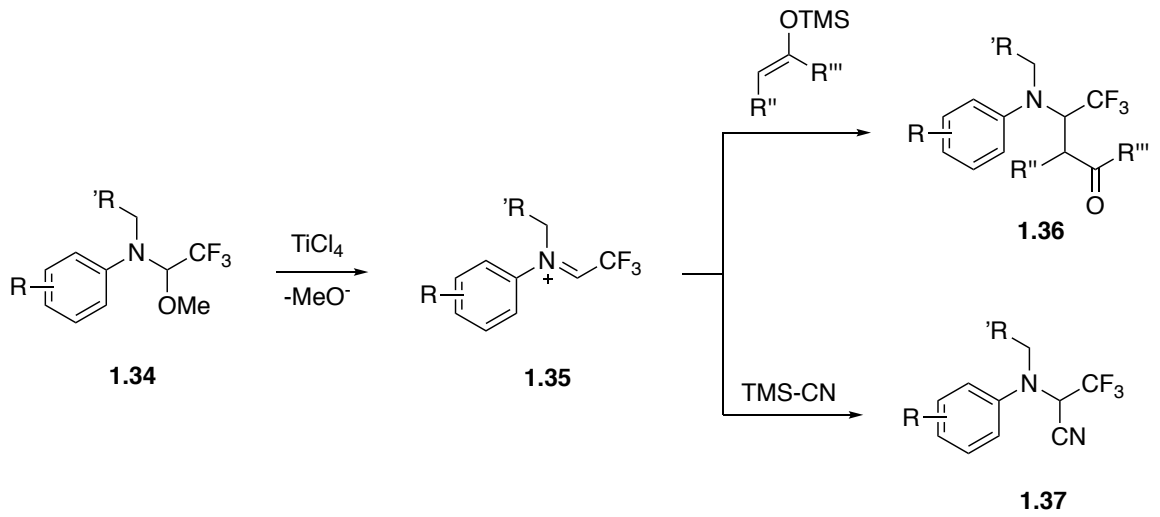


Figure 1.29 The trifluoroethylamine group as a synthetic intermediate.

N-2,2,2-trifluoroethylamines may also be converted into α-trifluoromethylated iminium cations **1.39** by oxidation with *m*CPBA and then a Polonovski-Potier reaction on the resulting *N*-oxide **1.38**.[190] Condensation with α-methylene ketones furnishes β-trifluoromethyl vinyl ketones **1.40**, with concomitant loss of the amino group.

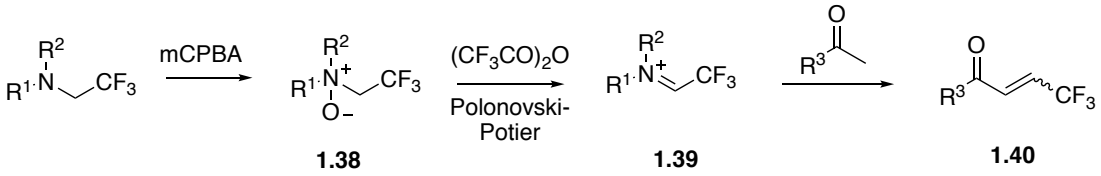


Figure 1.30 The trifluoroethylamine group as an intermediate to access β-trifluoromethyl vinyl ketones.

1.4 Trifluoroethylthiols

The trifluoroethylthio group is present in many bioactive molecules, particularly within the agrochemical community (**Figure 1.31**).[191,192]

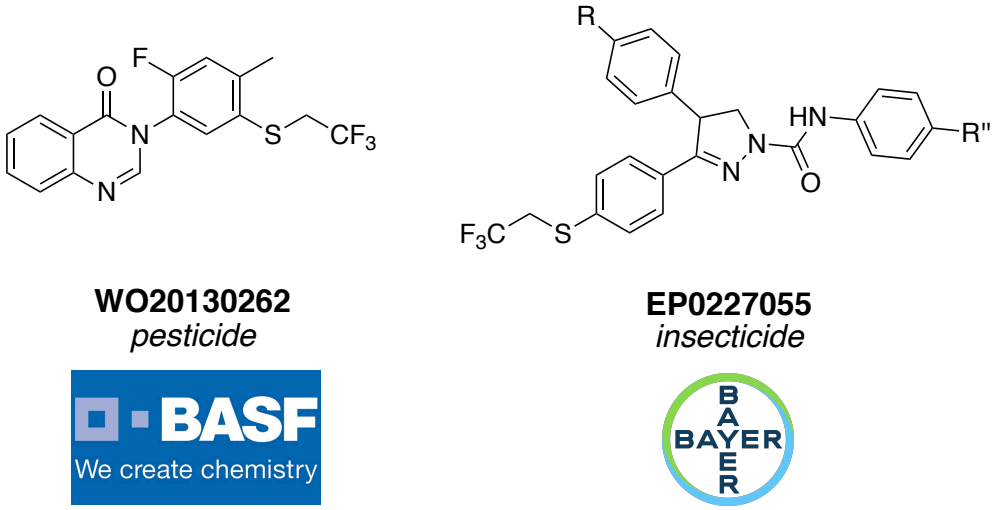


Figure 1.31 The trifluoroethylthio group in bioactive molecules.

Multiple routes to access the trifluoroethylthio group have been reported (**Figure 1.32**). The most common strategy for installing such a group being deprotonation of thiols and subsequent quenching with fluoroalkyl electrophiles (**A**).[193-196] Other methods involve the recombination of sulfur-centred radicals with carbon-centred radicals (**B**).[193,197-199] Acid-promoted insertion of trifluorodiazoethane into the S-H bond of thiophenols is also possible (**C**).[45,200] More recent developments in this field involve the remarkable one-pot synthesis of 2,2,2-trifluoroethylthiolated compounds from aryl halides, elemental sulfur and fluoroalkyls (**D**).[201] Less used methods include use of Umemoto's hypervalent iodine reagent (**E**).[81]

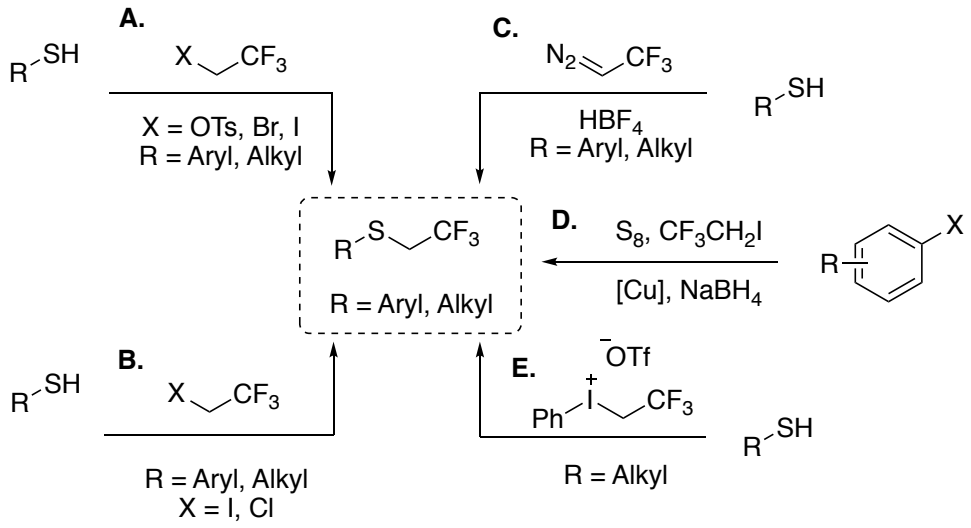


Figure 1.32 Methods of introducing the trifluoroethylthio group.

α-Substituted trifluoroethylthio groups are significantly less represented within the literature, with only two types of disconnection reported (**Figure 1.20**): nucleophilic displacement of α-trifluoromethyl benzylic sulfonates (**A**);[202-205] and Lewis acid-catalysed electrophilic aromatic substitution of aromatics *via* 2,2,2-trifluoro-thioethyl carbocation electrophiles (**B**).[206-208]

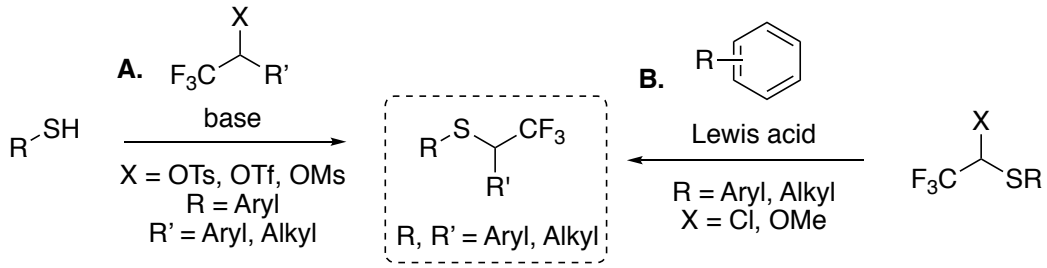


Figure 1.33 Methods of introducing the α-substituted trifluoroethylthio group.

Enantiopure α-branched trifluoroethylthio compounds are obtained either by nucleophilic substitution with enantiopure α-branched-2,2,2-trifluoroethylthiol starting materials,[209] or by chiral resolution techniques.

The trifluoroethylthio group is a versatile intermediate, with (2,2,2-trifluoroethyl)diphenylsulfonium triflate **1.41** being a precursor to the ylide **1.42**, used for the diastereoselective Johnson-Corey-Chaykovsky trifluoroethylidenation of aldehydes, olefins and imines to yield trifluoromethyl epoxides (**A**), cyclopropanes (**B**) and aziridines (**C**) respectively.[210-212] In the presence of iron catalyst, (2,2,2-trifluoroethyl)diphenyl-sulfonium triflate has recently been shown to generate trifluoromethylcarbene (:$CHCF_3$), which readily forms cyclopropanation products in the presence of olefins.[211] Furthermore, Baran and co-workers utilised zinc trifluoroethylsulfinate salts **1.43** to functionalise heterocycles (**D**).[213]

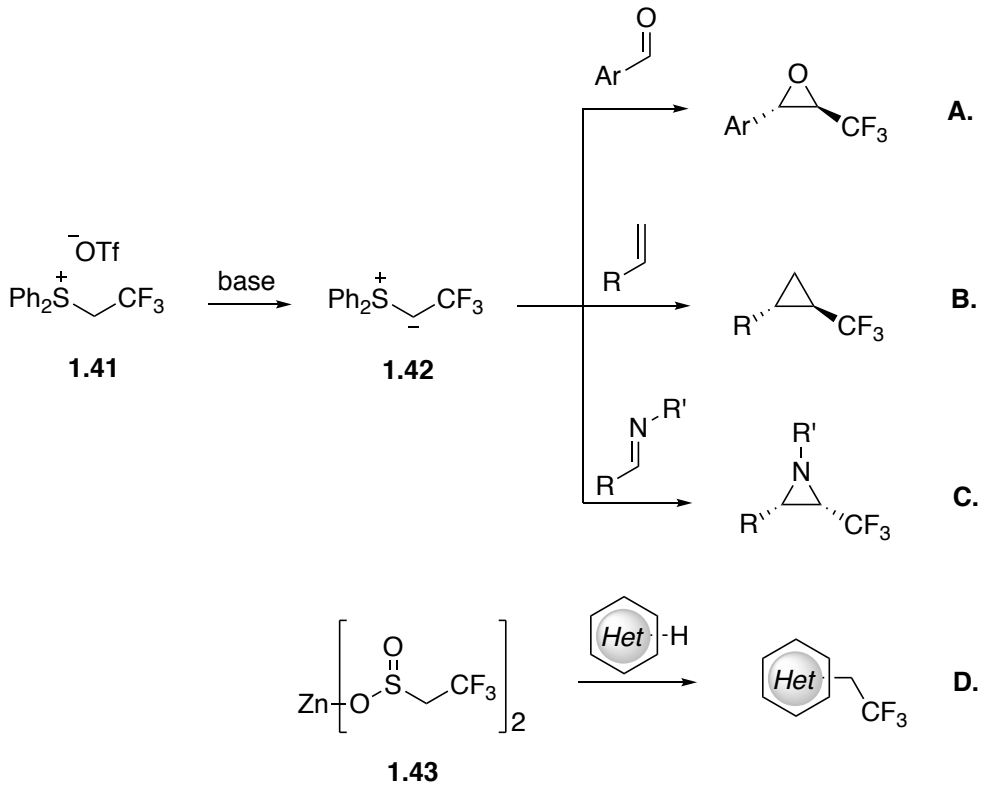
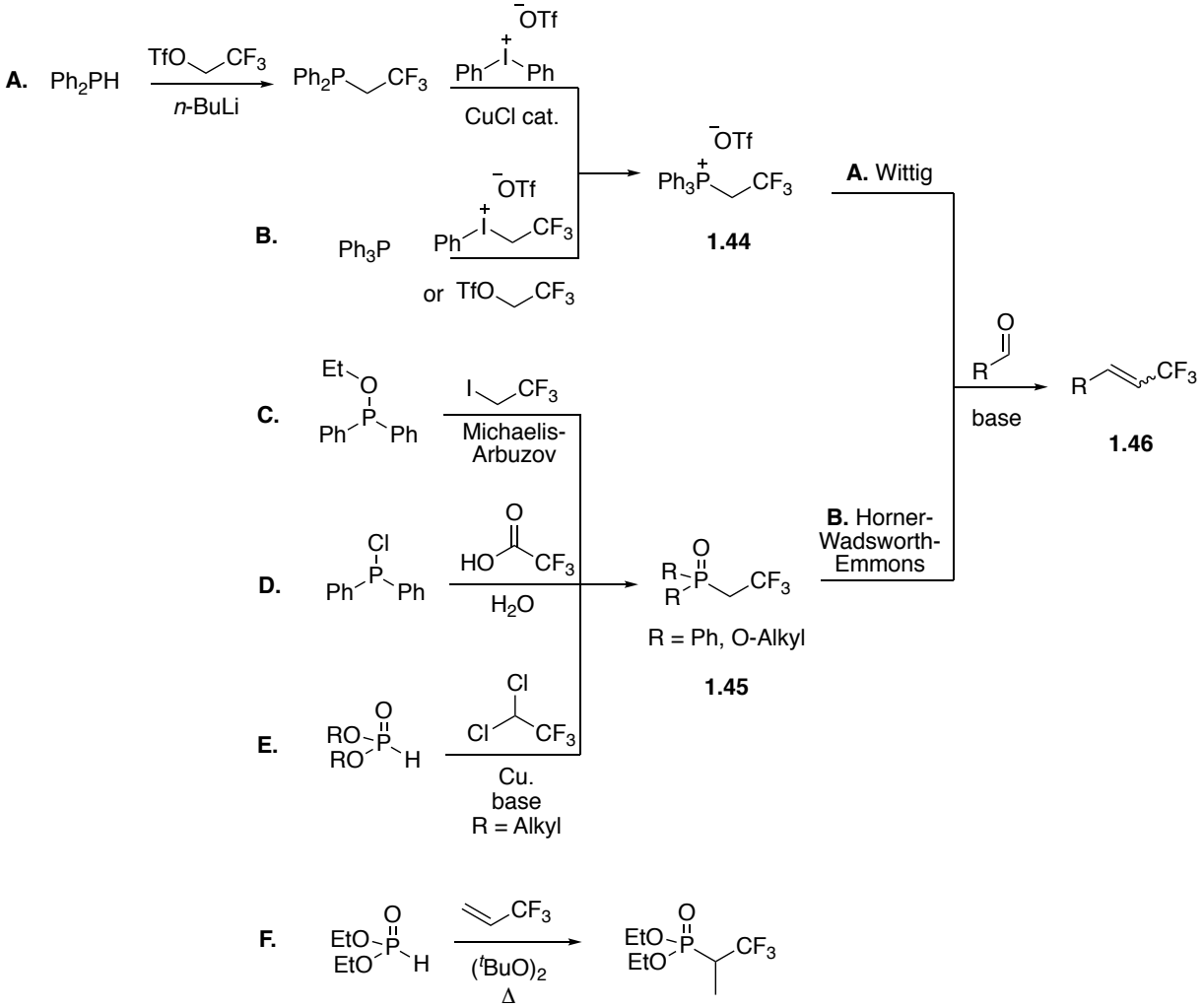


Figure 1.34 The trifluoroethylthio group as a synthetic intermediate.

1.4.4 The Phosphorous-Trifluoroethyl Group

Other heteroatom-trifluoroethyl motifs less frequently observed in the final drug molecule have justified synthetic value as synthetic intermediates. For example, 2,2,2-trifluoroethyl-phosphonates/phosphine oxides **1.45**, and phosphonium salts **1.44** are used extensively within the pharmaceutical and agrochemical industry for the generation of trifluoromethylated olefins **1.46** *via* a Horner-Wadsworth-Emmons (**B**),[214,215] and Wittig reactions (**A**).[216,217]



Scheme 1.35 Syntheses and use of trifluoroethyl phosphonates and phosphine oxides.

These valuable intermediates are accessed *via* a range of synthetic routes: quaternization of (trifluoroethyl)diphenylphosphane (**A**);[216,218] or trifluoroethylation of

triphenylphosphine (**B**)[216,217] to yield (trifluoroethyl)phosphonium salts **1.44**. (Trifluoroethyl)phosphonates/phosphine oxides **1.45** are made by: Michaelis-Arbuzov-type reactions from ethyl diphenylphosphinite (**1.35**) and fluoroalkylhalides (**C**);[214] reaction of chlorodiphenylphosphine with trifluoroacetic acid (**D**);[219-221] and the Cu-promoted reaction of 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) with dialkyl phosphites (**E**).[222] A radical reaction of 3,3,3-trifluoropropene with diethyl phosphate was also reported (**F**), although this yields both normal and reverse adducts and gives a range of telomers.[223]

1.4.5 Trifluoroethylboron Compounds

The trifluoroethylboron group was, until recently, an underexplored unit in organic chemistry. The first example of such a species dates from 1999 when Herbert Brown and co-workers worked on the rhodium-catalysed regioselective hydroboration of 3,3,3-trifluoropropene. They discovered that the regioselectivity of hydroboration, and subsequent oxidation, could be manipulated by the steric bulk of the borane – bulkier pinacolboranes yield primary fluoroalkyl alcohols *via* an anti-Markovnikov process (**B**), whereas less bulky catecholboranes furnish the Markovnikov product, secondary fluoroalkyl alcohols (**A**).[224] Dilman and co-workers reported the nucleophilic trifluoromethylation of bromomethyl borane (**C**).[225] The Molander group then disclosed a method of generating α-trifluoromethylated alkylboron compounds *via* an α-transfer mechanism between 2,2,2-trifluorodiazoethane and alkyl/aryl/allyl/alkynyl-boronic species (**D** & **E**),[226] a method he later elaborated on to generate vicinally bis(trifluoromethylated) alkylboron compounds through successive diazo α-transfer steps (**F**).[227]

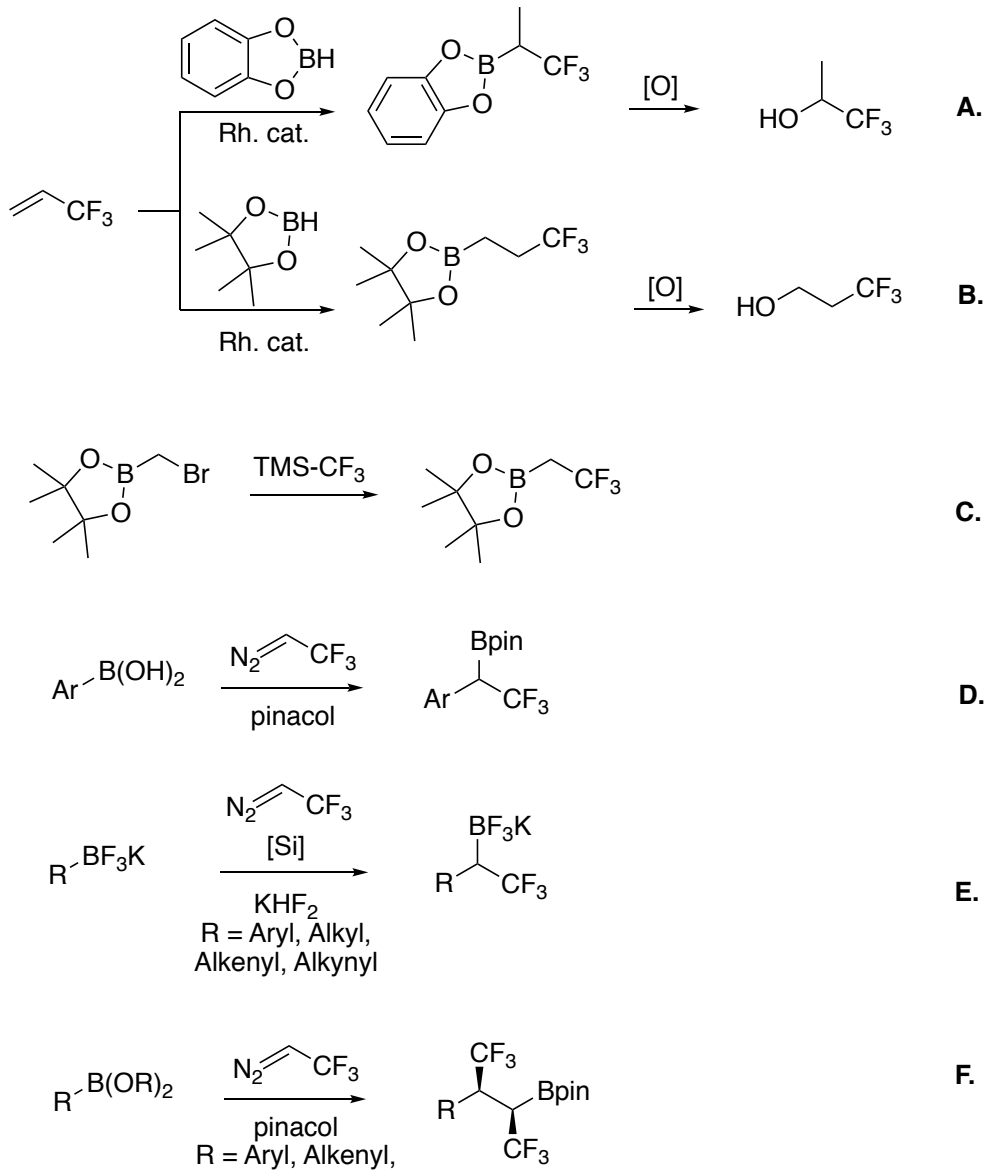


Figure 1.36 Syntheses of 2,2,2-trifluoroethylboron compounds.

Molander and co-workers cemented α-trifluoromethylated alkylboron compounds as viable synthetic intermediates by diverse product valorisation (**Figure 1.37**): Initially with oxidation (**A**); halodeboronation (**B**); protodeboronation (**C**); B-C insertion with ethyl diazoacetae (EDA) (followed by auto-protodeboronation) (**D**); B-F elimination (**E**); and stereoretentive Matteson homologation (**F**).[226,227] However, arguably the greatest contribution came when the same group developed a photoredox iridium/nickel dual catalytic cross-coupling between these α-trifluoromethylated alkylboron reagents and

(hetero)aryl bromides to yield 1,1-diaryl-2,2,2-trifluoroethanes (**G**); 60 % enantioemeric excess was achieved when utilising bioxazoline ligands.[228] This justified α-trifluoromethylated alkylboron reagents as viable cross-coupling partners – a non-trivial accomplishment as trifluoromethyl groups bound germinal to transition metals are prone to β-fluoride elimination.[229]

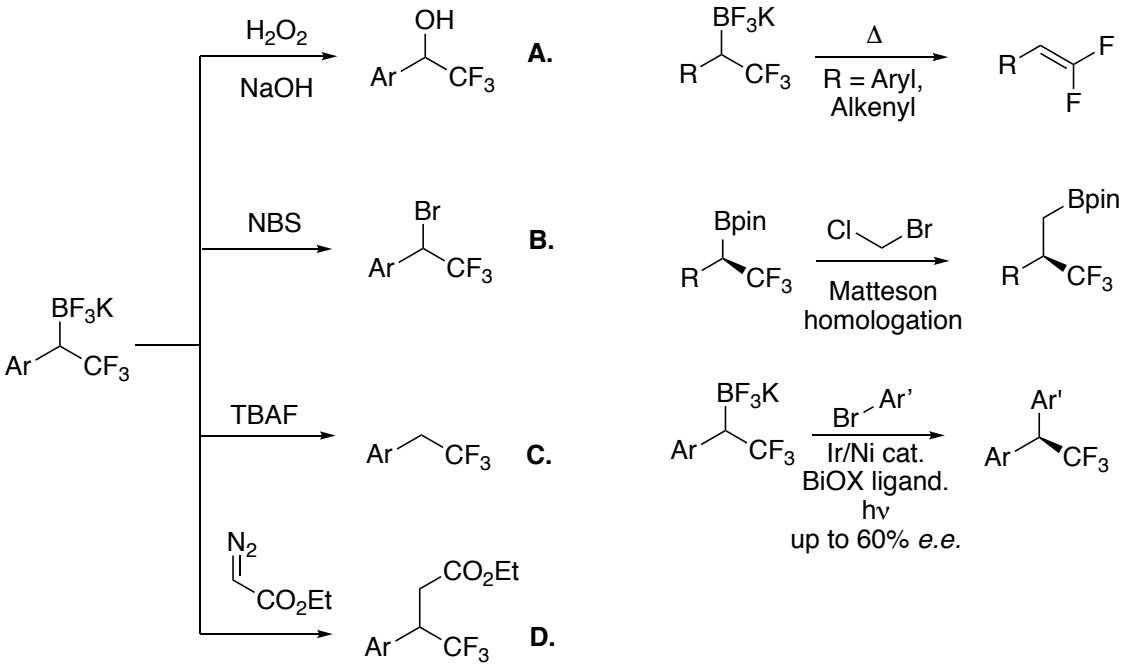


Figure 1.37 Synthetic utility of 2,2,2-trifluoroethylboron compounds.

1.4.6 Other Heteroatom-trifluoroethyl Compounds

Trifluoroethylsilanes

Fluoroalkylsilanes have seen a recent resurgence of interest for use in materials chemistry, with applications in lubricants, adhesives, self-cleaning coatings and for use in chromoatographic separation.[230] Despite this, routes to the 2,2,2-trifluoroethylsilane motif are limited in the literature to radical recombination resulting from the photolysis of hexafluoroacetone and tetramethylsilane (**A**),[231] and carbene insertion into the Si-H bond (**B**) (**Figure 1.38**).[74,232-234]

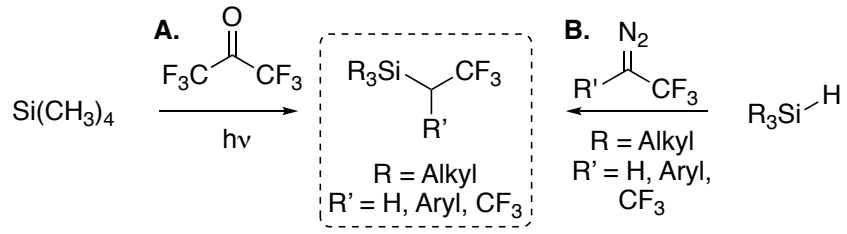


Figure 1.38 Reported synthesis of the 2,2,2-trifluoroethylsilane motif.

Trifluoroethylstannanes

Organotin chemistry occupies a vast field of organic chemistry,[235] however methods to access 2,2,2-trifluoroethylstannanes are limited to two disconnections; radical recombination of a trifluoromethyl radical resulting from the photolysis of hexafluoroacetone (**A**),[236] and carbene insertion into the Sn-H bond (**B**) (**Figure 1.39**).[237]

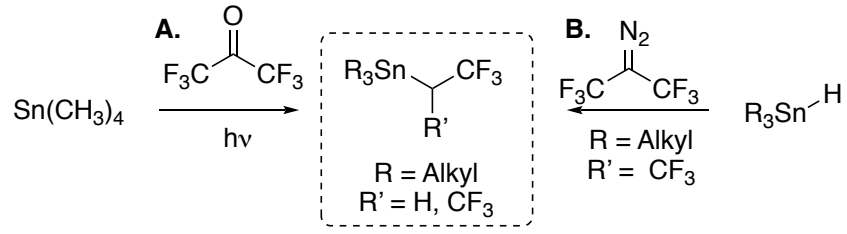


Figure 1.39 Reported syntheses of 2,2,2-trifluoroethylstannanes.

Trifluoroethylgermanes

Organogermanes have been explored as novel coupling partners with lower toxicity than organostannanes,[238-241] but only one example of trifluoroethylgermanes have been reported by the hydrogermylation of tetrafluoropropene (**Figure 1.40**).[242]

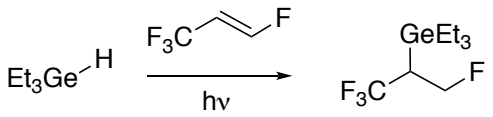


Figure 1.40 Reported synthesis of 2,2,2-trifluoroethylgermane.

CHAPTER 2

Heteroatom-Hydrogen Insertion using Trifluorodiazoalkanes

Chapter 2: Heteroatom-Hydrogen Insertion using Trifluorodiazoalkanes

2.1 Introduction

2.1.1 Diazo Compounds – Structure, Stability and Reactivity

Diazo compounds contain two linked nitrogen atoms with general formula $R^1R^2C{=}N_2$ (**Figure 2.1**); they are linear motifs which may be represented by two resonance structures – **2.1** and **2.2**. When the negative charge is unstabilised, for example, $R^1 = R^2 = H$ (diazomethane), these compounds are very reactive and explosive.[243] However, when diazo groups are located next to electron withdrawing groups – capable of stabilizing this negative charge – the compound is more stable and the chemical properties of the molecule are significantly different to those of simple diazo compounds.



2.1 **2.2**

Figure 2.1 Resonance structures of diazo compounds.

Hence, the vast majority of synthetic chemistry involving diazo compounds has centred around the use of α-diazocarbonyl compounds **2.3**, originating from the work of Curtius, who synthesised ethyl diazoacetate (EDA) by diazotisation of glycine in 1883.[244] Over the past century, the diazo functional group has proved itself as extremely versatile and capable of many transformations, such as: the Wolff rearrangement **A**, cyclopropanation reactions **B**, the Buchner reaction **C**, aromatic substitution reactions **D**, C-H insertion **E**, heteroatom-H insertion (XHI) **F**, ylide formation **G**, α,α-substitution reactions **H**, [3+2]

cycloadditions **I**, β-hydride elimination (Bamford-Stevens-type) **J**, homologation of aldehydes **K** and oxidation reactions **L** (**Figure 2.2**).[245,246]

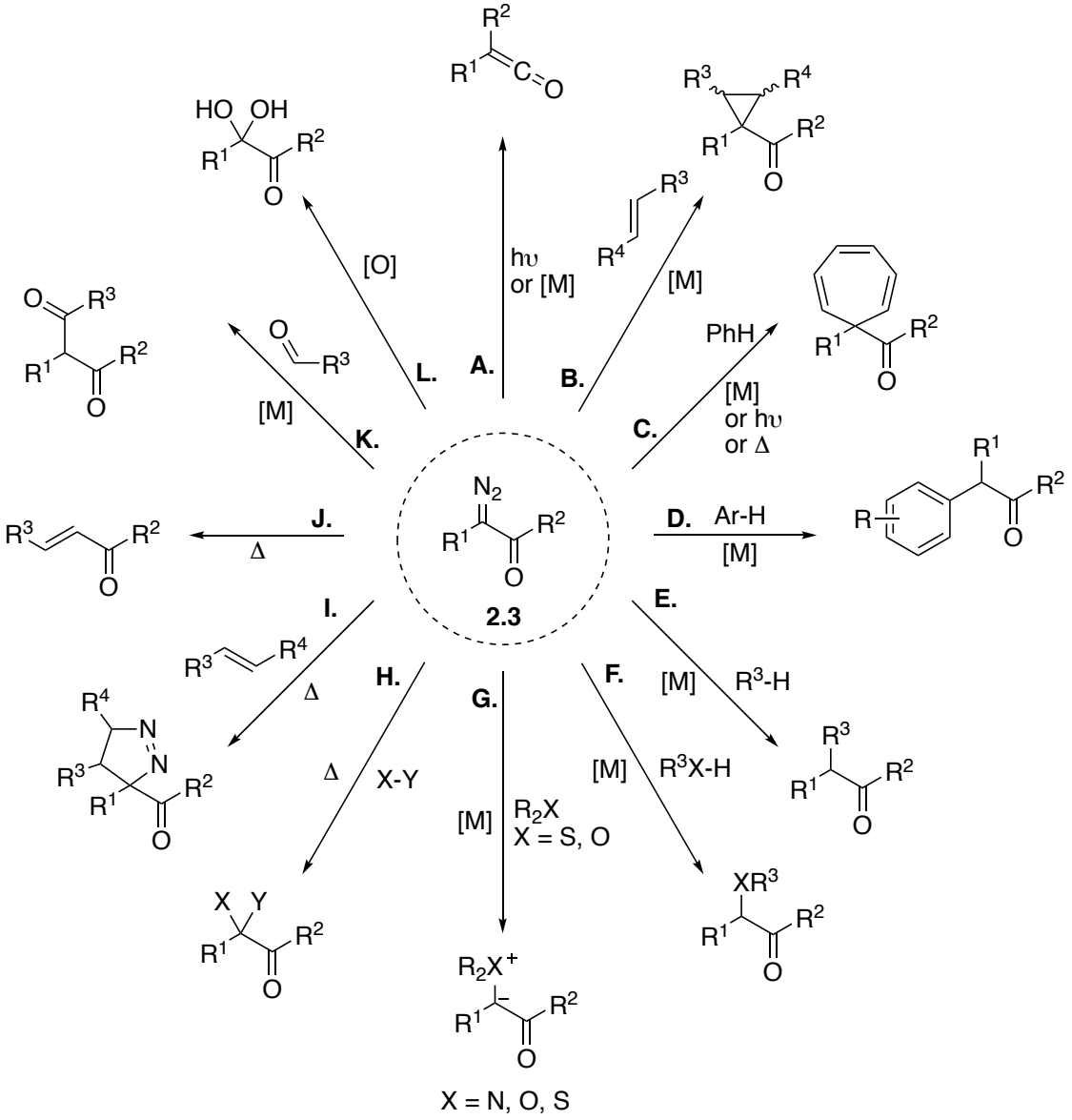


Figure 2.2 Reactions of α-diazocarbonyl compounds.

2.1.2 Trifluorodiazoethane

Introduction of a trifluoromethyl group to a diazo functionality also significantly increases the stability of the compound compared with non-fluorinated alkyl diazo compounds. For example, 2-diazopropane **2.4** exhibits pronounced instability, readily dimerising or undergoing a Bamford-Stevens elimination, even in solution at room temperature, to

yield tetramethylethylene **2.5** and propene **2.6** respectively – with potentially explosive consequences (**Figure 2.3**).[247,248]

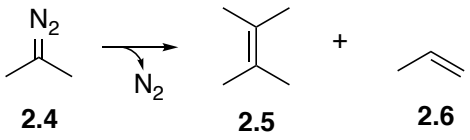


Figure 2.3 Instability of 2-diazopropane.

Replacement of one methyl group with a trifluoromethyl functionality increases the stability of the molecule, reducing side reactions such as dimerisation **2.8**;[249] replacement of both methyl groups further increases the molecular stability, with perfluorodiazopropane **2.9** neither impact or static sensitive, and capable of being stored neat for a number of weeks before any degradation is observed (**Figure 2.4**).[200,250]

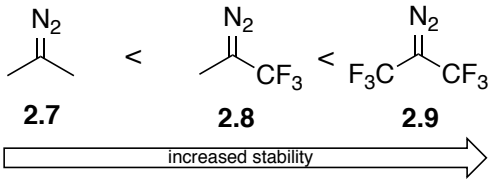


Figure 2.4 Increased stability of fluoroalkyldiazo compounds.

The first example of such a molecule dates from 1943 by Gilman and Jones, who made trifluorodiazoethane **1a** by treating trifluoroethylamine with nitrous acid (**Figure 2.5**).[251]

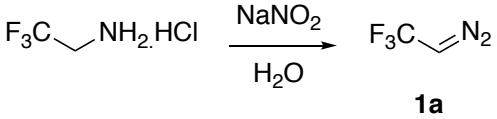


Figure 2.5 Synthesis of 2,2,2-trifluorodiazoethane **1a**.

Since Gilman and Jones' pioneering work, significant methodology development has occurred utilising trifluorodiazoethane **1a** as a reagent (**Figure 2.6**). These

transformations include: reactions with boronic species to yield trifluoroethylated products *via* α-transfer mechanism **A**;[252,253] cyclopropanation reactions **B**;[254,255] carbonyl homologation **C**;[256,257] heteroatom-hydrogen insertion reactions **D**;[45,74,77,258] acid-promoted nucleophilic substitutions **E**;[259] [3+2] cycloadditions **F**;[260,261] homologation of aldehydes **G**;[257] epoxidation[200] and aziridination **H**.[262,263]

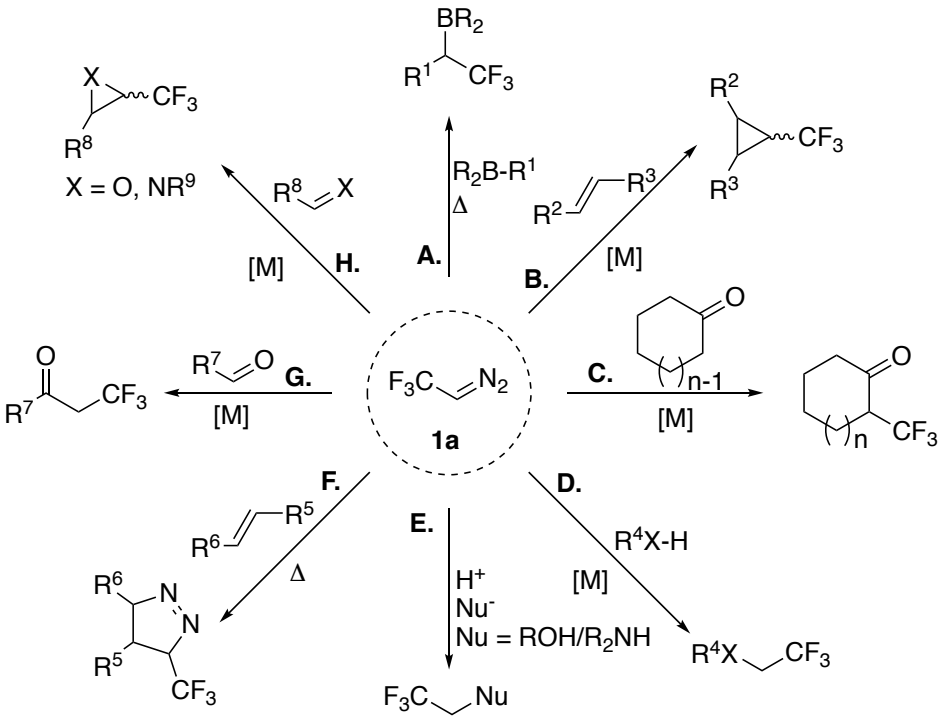


Figure 2.6 Reactions of 2,2,2-trifluodiazoethane **1a**.

Notably, a disproportionate amount of this literature has been developed since 2010, when Carreira and co-workers developed a method of generating **1a** *in situ* (**Scheme 2.1**);[264] prior to this, trifluorodiazoethane **1a** – a volatile, toxic and explosive reagent – had to be distilled from aqueous media. Notwithstanding the procedural obstacles, handling of neat solution of **1a** is dangerous, and Carreira's contribution significantly expanded the use of **1a** as a reagent. Building on Carreira's work, continuous flow technology has been used to generate **1a** safely for larger-scale industrial processes, validating this substance as a viable synthetic reagent.[265]

2.1.3 α-Substituted Trifluorodiazoethane

Trifluorodiazoethane **1a** is an acceptor only diazo compound, and thus exhibits great reactivity and poor selectivity.[266,267] Donor/acceptor diazo compounds are significantly more stable, with α-substituted 1-aryl-2,2,2-trifluoro-1-diazoethanes being significantly less reactive than **1a**, as well as offering a platform for introducing increased complexity in the form of stereocentre (**Figure 2.7**). α-Substituted 1-aryl-2,2,2-trifluoro-1-diazoethanes may be made *via*: interrupted Bamford-Stevens reactions **A**;[268,269] diazotization of 1-aryl-2,2,2-trifluoroethylamines **B**;[270,271] oxidation of α,α,α-trifluoroacetophenone hydrazines **C**;[249,270] and rearrangement of diazirines **D**.[272]

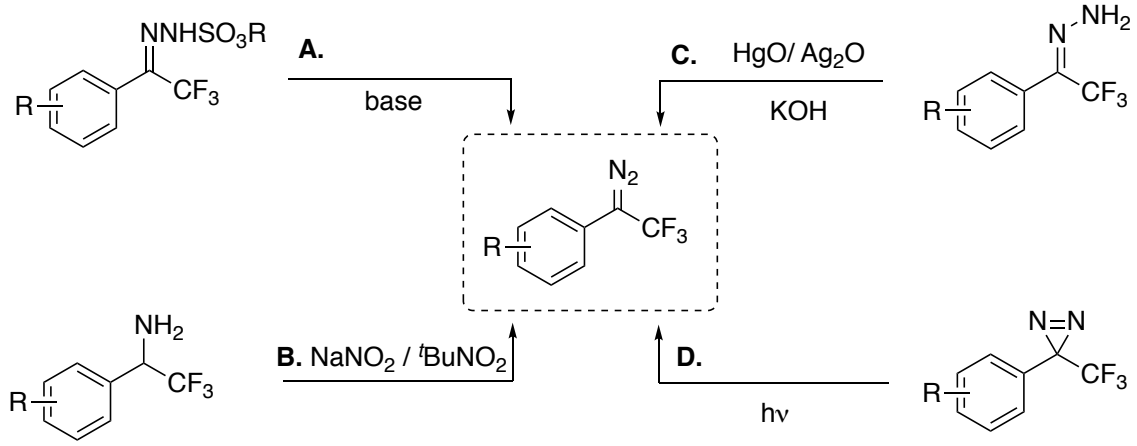


Figure 2.7 Generation of 1-aryl-2,2,2-trifluoro-1-diazoethanes.

1-Aryl-2,2,2-trifluoro-1-diazoethanes have been explored in various transformations (**Figure 2.8**): α,α-funtionalisation **A**;[268,273] cyclopropanation **B**;[274-277] [3+2] cycloadditions **C**;[271,278] synthesis of trifluoromethylated alkenes *via* Pd-carbene migratory insertion **D**;[279] synthesis of allenes *via* Cu(I)-catalysed coupling of diazoalkanes with terminal alkynes **E**;[280] and heteroatom-hydrogen insertions **F**.[233,281]

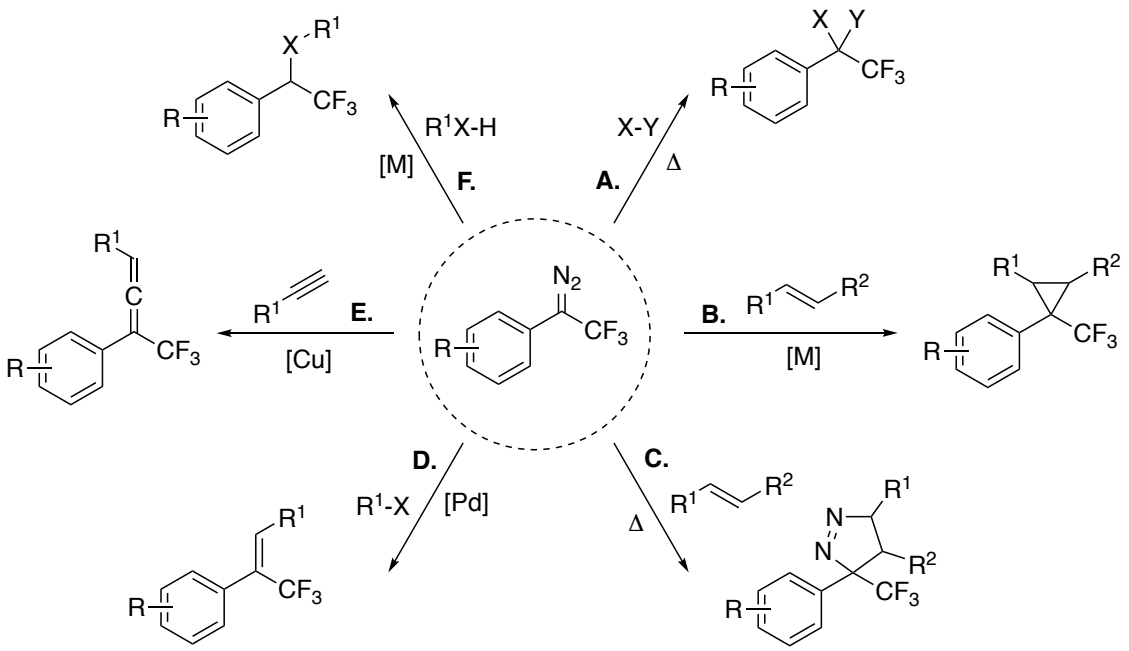


Figure 2.8 Reactions of 1-aryl-2,2,2-trifluoro-1-diazoethanes.

2.1.4 Limitations of XHI reactions with Fluorinated Diazo Compounds

Reported heteroatom-hydrogen insertion reactions (XHI) with 2,2,2-trifluorodiazoethane **1a** are limited by several factors (**Figure 2.9**). Firstly, most synthetic pathways involve distillation of 2,2,2-trifluorodiazoethane,[45,74-77,200,282] which is not only operationally cumbersome but potentially dangerous, with one report disclosing that an explosion occurred when vacuum was suddenly lost during distillation;[200] secondly, most procedures either suffer from exceptionally long reaction times (up to five weeks),[74] or the use of tetrafluoroboric acid catalyst,[45,77] rendering the method incompatible with N-H insertion, as the catalyst is neutralised by the substrate. In fact, only one example of N-H insertion has been reported to date, but this method is restricted to anilines.[258]

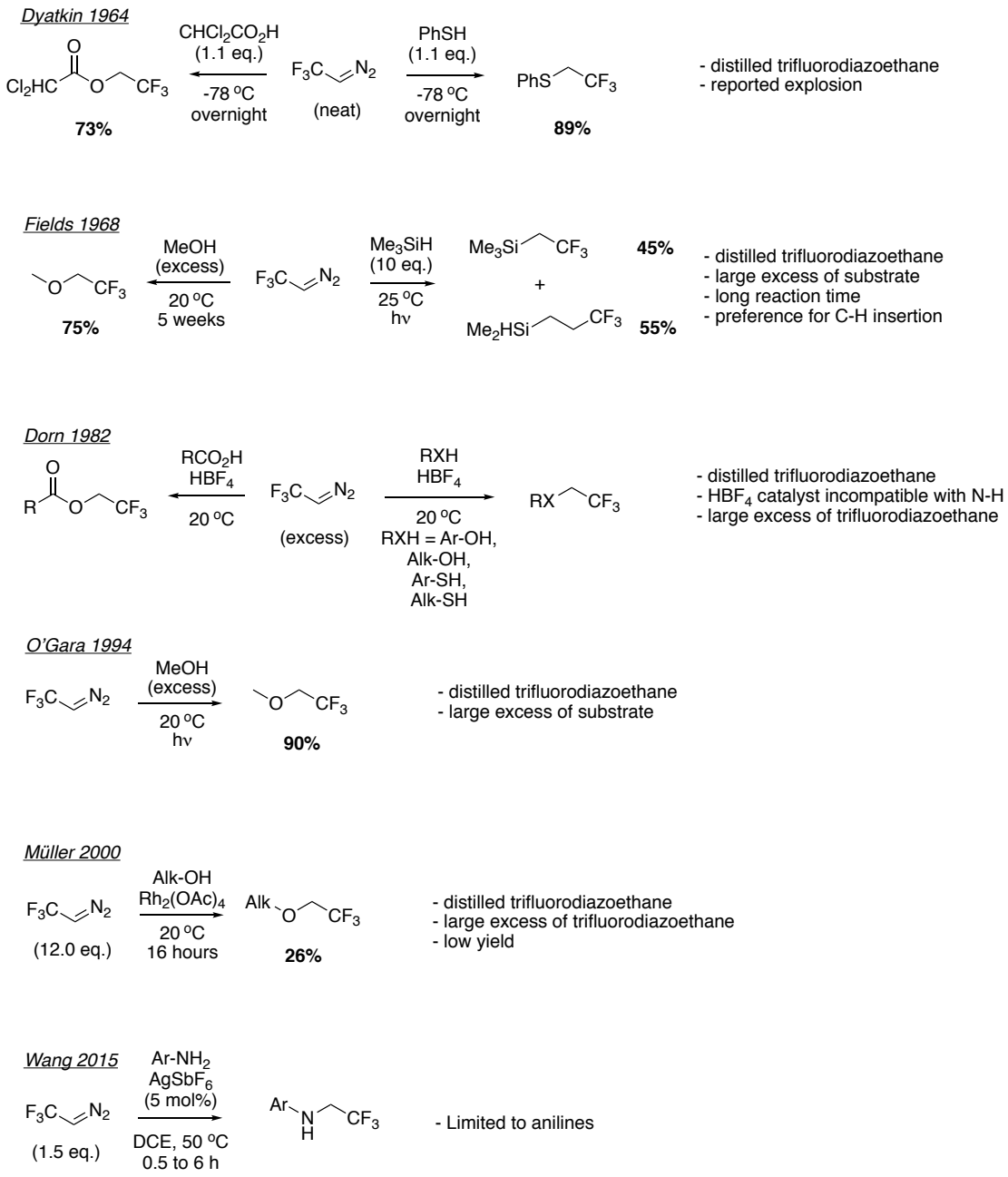


Figure 2.9 Reported procedures for heteroatom-hydrogen insertion using 2,2,2-trifluorodiazoethane **1a**.

Regarding α-substituted 1-aryl-2,2,2-trifluoro-1-diazoethanes; at the commencement of this research no heteroatom-hydrogen insertion reaction had been reported. Since disclosing this material one example of N-H[281] and Si-H[233] insertion have been reported, neither of them offering a system capable of delivering enantioenriched products.

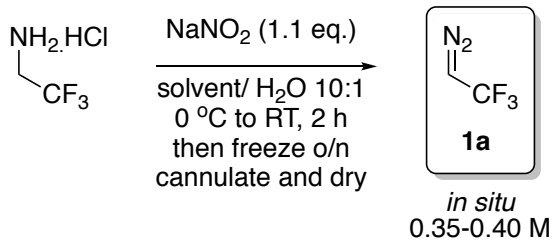
2.2 XHI with Trifluorodiazoethane

2.2.1 Reaction Development

Preliminary investigations conducted with assistance from Dr. Benoît Liégault.

Given the importance of the heteroatom-trifluoroethyl motif (**chapter 1**), and the limitations with current heteroatom-hydrogen insertion reactions (XHI) with 2,2,2-trifluorodiazoethane **1a**, initial studies focused on achieving such an XHI that improved on previously disclosed methods based on the following criteria: operational simplicity (no need to distil **1a**); operational safety (no need to handle neat **1a**); applicable to a broad range of heteroatom substrates; reasonable stoichiometry and acceptable reaction times.

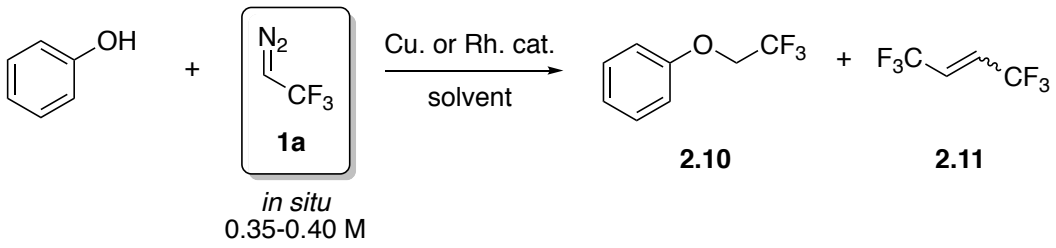
This study began with the preparation of 2,2,2-trifluoro-1-diazoethane **1a** *via* diazotisation of commercially available 2,2,2-trifluoroethylamine hydrochloride according to the procedure disclosed by Morandi and Carreira.[264] In this procedure, upon reaction completion, the organic solvent/aqueous biphasic mixture was cooled below zero to enable water to freeze out. The resulting 2,2,2-trifluoro-1-diazoethane **1a** – fully soluble in the organic layer – was then cannulated from the vessel into a separate flask containing a drying agent (K_2CO_3) and left for at least 1 h prior to use. An aliquot of the solution was taken to determine the concentration by ^{19}F NMR (according to an internal reference $PhCF_3$). Typically, 0.35-0.40 M solution of 2,2,2-trifluoro-1-diazoethane **1a** in toluene or dichloromethane was obtained (**Scheme 2.1**).



Scheme 2.1 Synthesis of 2,2,2-trifluoro-1-diazoethane **1a**.

Given the large body of work on copper- and rhodium-catalysed XHI reactions with α-diazoesters,[283] initial studies were limited to these transition-metals to probe the reactivity of 2,2,2-trifluoro-1-diazoethane **1a** with various substrates. Furthermore, motivated by the biological importance of the trifluoroethoxy unit (**chapter 1**), this project began by exploring the feasibility of insertion into the O-H bond of phenol (**Table 2.1**). Disappointingly, no such XHI product **2.10** was observed – instead, in all cases, only hexafluorobutene **2.11** was observed by NMR of the crude material as a 1:1 mixture of *E* and *Z* isomers, with complete consumption of 2,2,2-trifluorodiazoethane **1a** after 15 minutes.

Table 2.1 Initial screening of **21a** against O-H insertion to phenol.

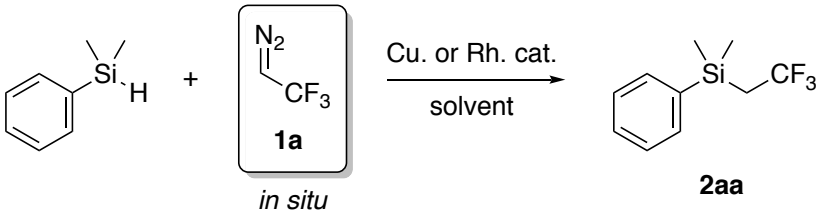


Entry	Catalyst (mol%)	Solvent	Yield 2.10/ %[a]
1	$Rh_2(OAc)_4$ (5)	CH_2Cl_2	0
2	$Rh_2(OAc)_4$ (5)	2,2-DMB	0
3	$Cu(CH_3CN)_4PF_6$ (5)	CH_2Cl_2	0
4	$Cu(CH_3CN)_4PF_6$ (5)	2,2-DMB	0

Reaction conditions: At room temperature, **1a** (0.7 mmol, 2.3 eq.) in stock solution of solvent (0.35-0.4 M) was added in one portion to solution of PhOH (0.3 mmol, 1.0 eq.) dissolved in the same solvent (0.6 M). [*a*] Yield determined by ^{19}F NMR spectroscopy with trifluorotoluene as internal reference. 2,2-DMB = 2,2-dimethylbutane.

When **1a** was probed against Si-H insertion, the desired XHI product **2aa** was observed, albeit in modest yield (**Table 2.2, entries 1-4**). These preliminary results indicated that $Cu(CH_3CN)_4PF_6$ was a superior catalyst to $Rh_2(OAc)_4$, and dichloromethane was superior to 2,2-dimethylbutane as solvent. 2,2,2-Trifluorodiazoethane **1a** had been completely consumed, with only hexafluorobutene **2.11** observed by crude NMR. Formation of hexafluorobutene **2.11** – formed by dimerization of two molecules of trifluoromethyl carbene – may be prevented by slow addition (30 minutes) of 2,2,2-trifluorodiazoethane **1a** using a syringe pump (**entry 5**). With the new slow-addition protocol, catalyst loading could be reduced to 2 mol% (**entry 7**), but product **2aa** was formed in lower yield when this was further reduced to 1 mol% (**entry 8**). Changing the oxidation state of the catalyst proved detrimental (**entry 9**) – this is consistent with the work of Kochi and co-workers who proved that even in cases of nominal catalysis by Cu(II) or Cu(0), Cu(I) is the catalytically active oxidation state in copper-carbenoid chemistry, with Cu(II) first being reduced to Cu(I) by sacrificial use of the diazo species before the carbenoid is formed.[284] Changing the solvent to toluene (**entry 6**) also negatively affected the yield. Furthermore, no reaction took place with $AgSbF_6$ (5 mol%) in 1,2-dichloroethane (**entry 10**) – reaction conditions identified as optimal for the *N*-trifluoroethylation of anilines by Wang and co-workers.[258] As expected, the catalyst was essential for Si-H insertion (**entry 11**).

Table 2.2 Initial screening of **1a** against Si-H insertion.



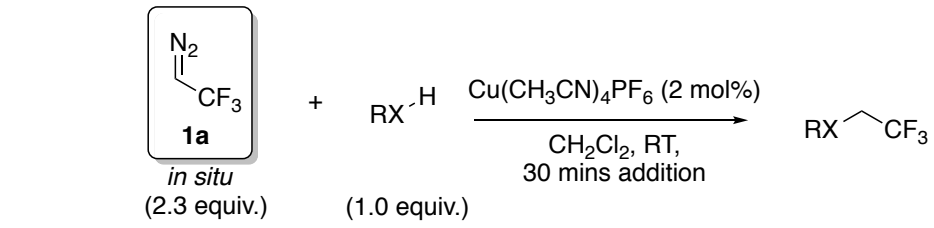
Entry	Catalyst (mol%)	Solvent	Conditions[a]	Yield 2aa/ %[b]
1	$Rh_2(OAc)_4$ (5)	CH_2Cl_2	A	16
2	$Rh_2(OAc)_4$ (5)	2,2-DMB	A	15
3	$Cu(CH_3CN)_4PF_6$ (5)	CH_2Cl_2	A	44
4	$Cu(CH_3CN)_4PF_6$ (5)	2,2-DMB	A	34
5	$Cu(CH_3CN)_4PF_6$ (5)	CH_2Cl_2	B	87
6	$Cu(CH_3CN)_4PF_6$ (5)	toluene	B	61
7	$Cu(CH_3CN)_4PF_6$ (2)	CH_2Cl_2	B	(88)
8	$Cu(CH_3CN)_4PF_6$ (1)	CH_2Cl_2	B	61
9	$Cu(OTf)_2$ (2)	CH_2Cl_2	B	32
10[c]	$AgSbF_6$ (5)	DCE	B	0
11	-	CH_2Cl_2	B	0

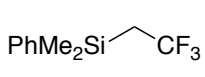
Reaction conditions: At room temperature, **1a** (0.7 mmol, 2.3 eq.) in stock solution of solvent (0.35-0.4 M), was added to solution of Me_2PhSiH (0.3 mmol, 1.0 eq.) dissolved in the same solvent (0.6 M). [*a*] Conditions A: manual addition of **1a** in one portion; conditions B: slow addition of **1a** over 0.5 h with a syringe pump. Reaction deemed to be complete once orange colour of **1a** no longer visible and no further nitrogen gas is evolved (typically shortly after addition is complete). [*b*] Yield determined by ^{19}F NMR spectroscopy with trifluorotoluene as internal reference. Values in parenthesis indicate yield of isolated product. [*c*] Reaction performed at 60 ^{o}C. 2,2-DMB = 2,2-dimethylbutane.

The optimal reaction conditions therefore consist of treating dimethylphenylsilane with an excess of 2,2,2-trifluorodiazoethane **1a** (2.3 eq.) in dichloromethane at room temperature in the presence $Cu(CH_3CN)_4PF_6$ (2 mol%) – with the rapid reaction typically complete shortly after addition of **1a** (30 minutes).

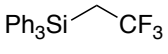
2.2.2 Scope and Limitations

The optimal conditions for reaction with **1a** were probed against a range of substrates – possessing a variety of different heteroatoms – for XHI (**Table 2.3**). Pleasingly, Si-H insertion of more sterically demanding triphenylsilane was successful, and led to product **2ab** in 77 % yield. Diphenylphosphine oxide and dimethylphosphonate also reacted under Cu(I) catalysis to afford **3aa** and **3ab** in 89 and 33 % yield, respectively, thereby establishing the feasibility of P-H insertion. The reaction tolerates a range of aryl, heteroaryl, and alkyl thiols, thus leading to the 2,2,2-trifluoroethyl-substituted sulfides **4aa-4al** in up to 90 % yield. Triphenylphosphine borane is a suitable substrate and was converted into the B-H insertion product **5aa** in 52 % yield. Under the standard reaction conditions, the reaction of 2,2,2-trifluoro-1-diazoethane with 4-methoxyaniline led to the double insertion product **6aa**. The generality of the reaction is striking, with this system successfully achieving insertion into five different heteroatom-hydrogen bonds: Si-H, P-H, S-H, B-H, and N-H. It is worth pointing out that the system did not offer a route to successful C-H insertion, even with activated substrates (**2.14** and **2.15**).[285] Compound **2aa** synthesised by Dr. Benoît Liégault. Compound **6aa** synthesised by Dr. David Grassi.

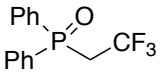




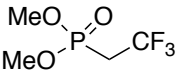
2aa[a]
88%



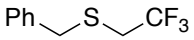
2ab
77%



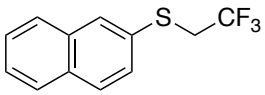
3aa
89%



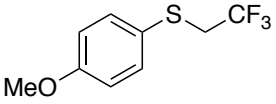
3ab
33%



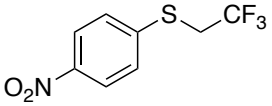
4aa
78%



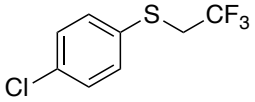
4ab
79%



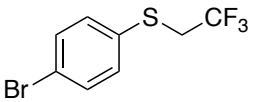
4ac
90%



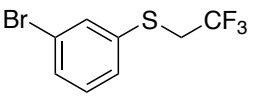
4ad
87%



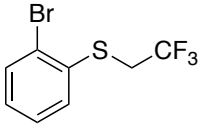
4ae
69%



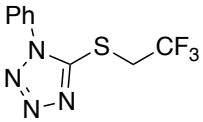
4af
86%



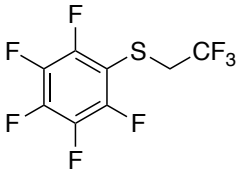
4ag
74%



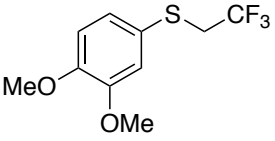
4ah
34%



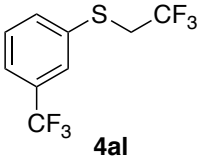
4ai
58%



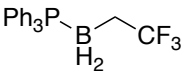
4aj
24%



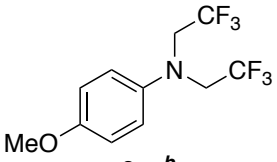
4ak
56%



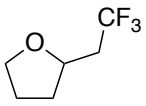
4al
22%



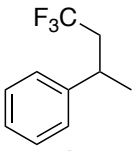
5aa
52%



6aa[b]
38%



2.14
0%



2.15
0%

Scheme 2.3 Scope of XHI with 2,2,2-trifluorodiazoethane **1a**. Yields given are for the isolated product. [*a*] Compound synthesised by Dr. Benoît Liégault. [*b*] Compound synthesised by Dr. David Grassi.

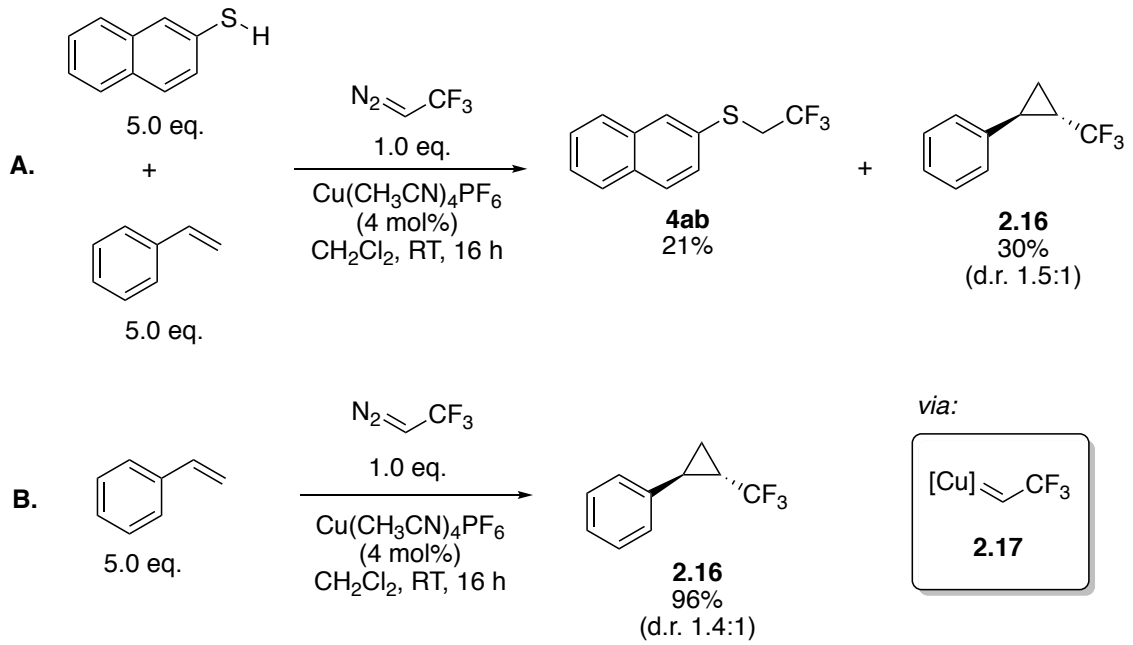
Since this work has been disclosed,[286] Sivasankar and co-workers have shown that, under copper-catalysed conditions, both α-diazo esters and α-substituted trifluorodiazoethanes will chemoselectively insert into the N-H bond over the O-H bond, with no O-H insertion being observed.[281,287] These results are consistent with the results disclosed above. However, O-H insertion with α-diazo esters under copper-bisoxazoline ligands have been reported.[288] These seemingly conflicting outcomes indicate that changes in the diazo reagent – substituting an ester for a trifluoromethyl functionality – can have a profound effect on a XHI reaction.

2.2.3 Mechanistic Studies

Mechanistic studies performed by Dr. Janis Veliks.

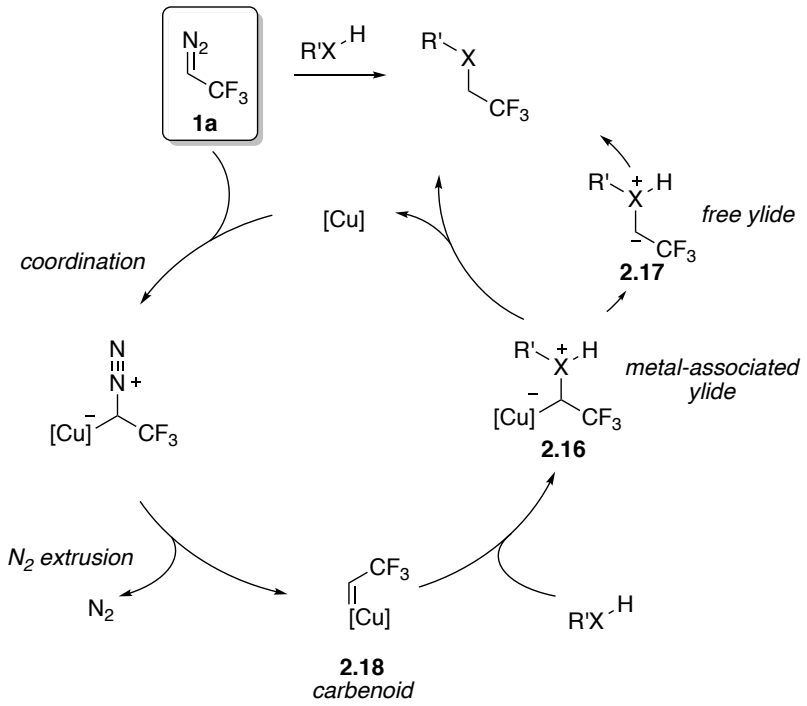
Copper-catalysed XHI reactions are thought to proceed *via* highly reactive metal-carbenoid intermediates.[283,284,289] With tailor made anionic ligands, copper(I)-carbenoids may be stabilised sufficiently to be detected in solution and fully characterised by spectroscopic means.[290] Isolation of these highly reactive intermediates is challenging, however, there are a small number of examples of the isolation and full characterisation of a copper(I)-carbenes, including X-ray crystal structures.[291,292] Indirect evidence for the existence of a copper(I)-carbenoid intermediate may be gained by spiking the reaction with an alkene – copper(I)-carbenoids rapidly undergo cyclopropanation reactions in the presence of olefins.[293] If cyclopropanation is faster than XHI, competition experiments between substrate and an olefin may provide qualitative evidence for the existence of the carbenoid intermediate. Hence, to give insight into the reaction mechanism,

competition experiments were performed; with an equimolar excess of substrate and styrene; formation of the cyclopropanation product **2.16** – indicative of a metal-carbenoid intermediate – outcompeted that of the XHI product **4ab** (**Scheme 2.4**). In the absence of substrate, the cyclopropanation product was formed in almost quantitative yield **2.16**. These results indicate the relevance of a copper-carbenoid species **2.17** in the catalytic cycle.



Scheme 2.4 Competition experiments to elucidate the reaction intermediate. Mechanistic studies performed by Dr. Janis Veliks.

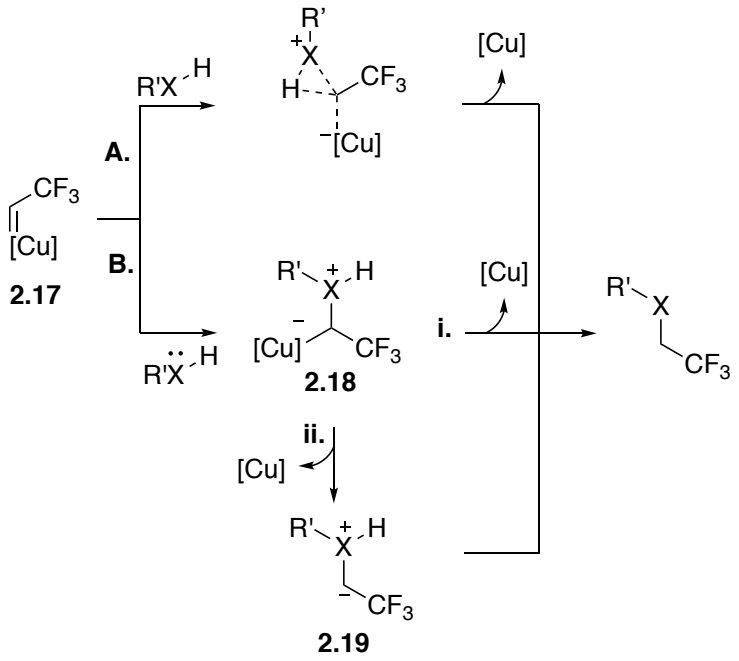
Such a catalytic cycle involves coordination of the negatively polarised carbon of the diazo substrate to the Lewis acidic free copper as the first productive step. Loss of nitrogen from the resulting intermediate then delivers the copper-carbenoid **2.17** (**Scheme 2.5**).



Scheme 2.5 Proposed catalytic cycle for copper-catalysed insertion into heteroatom-hydrogen bonds.

The carbenoid species then reacts with the substrate to form the XHI product and liberate the copper catalyst (**Scheme 2.6**); however, the exact pathway is highly dependent on several factors. It is generally accepted that insertions into X-H bonds bearing no lone-pair electrons on the X atom (eg. carbon, silicon) proceed *via* a concerted mechanism **A**, whereas insertions into X-H bonds bearing lone-pair electrons (eg. oxygen, nitrogen, sulfur) proceed *via* an ylide type intermediate mechanism **B**.[283,288] Further complicating matters is the fact that collapse of the ylide may proceed *via* either a metal-bound intermediate **B.i**., or a free-ylide **B.ii.** The preference for pathway **i** or **ii** may be influenced by the electronic properties of substituents on both the diazo compound and the substrate: electron-withdrawing substituents on the diazo compound, or electron-donating substituents on the substrate would likely stabilize free ylide **2.19** and thus favour the free-ylide process **B.ii**.[288] The exact pathway has little importance for

the production of achiral or racemic material, however understanding of the reaction pathway is of paramount importance when designing asymmetric XHI reactions and will be discussed later in this chapter.

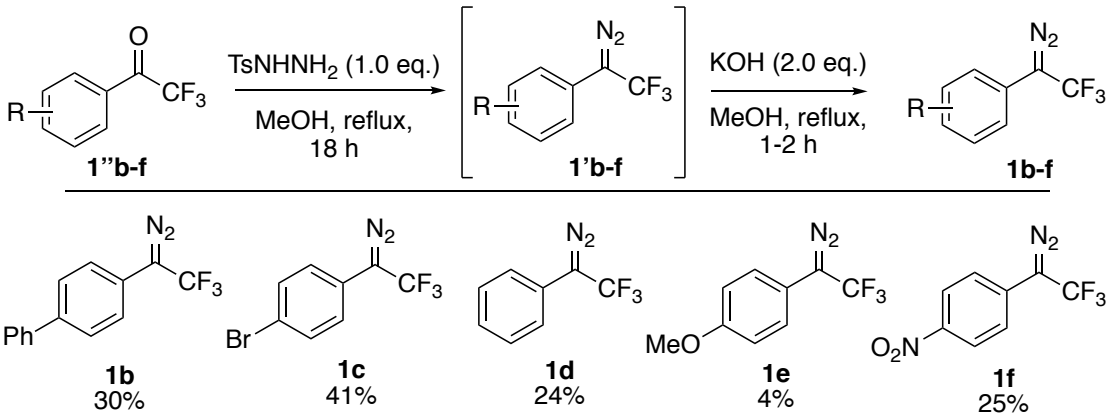


Scheme 2.6 Concerted **A**, metal-bound stepwise **B.i** and free ylide stepwise **B.ii.** decomposition of carbenoid intermediate.

2.3 XHI with α-Substituted Trifluorodiazoethanes

2.3.1 Scope and Limitatons

The broad scope of this methodology encouraged further studies on the installation of branched trifluoroalkyl fragments. The starting materials for this study – aryl-substituted 2,2,2-trifluorodiazoethanes – were prepared according to previously reported literature procedures: condensation of trifluoromethyl ketones with *para*-toluenesulfonyl hydrazide generates trifluoromethylated tosyl hyrazones, which, in the presence of KOH, undergo an interrupted Bamford-Stevens elimination to yield the desired 2,2,2-trifluorodiazoethanes (**Scheme 2.7**).[269,273,275,279] The resulting diazo products **1b-f** are volatile and significant material was lost whilst removing solvent *in vacuo*.

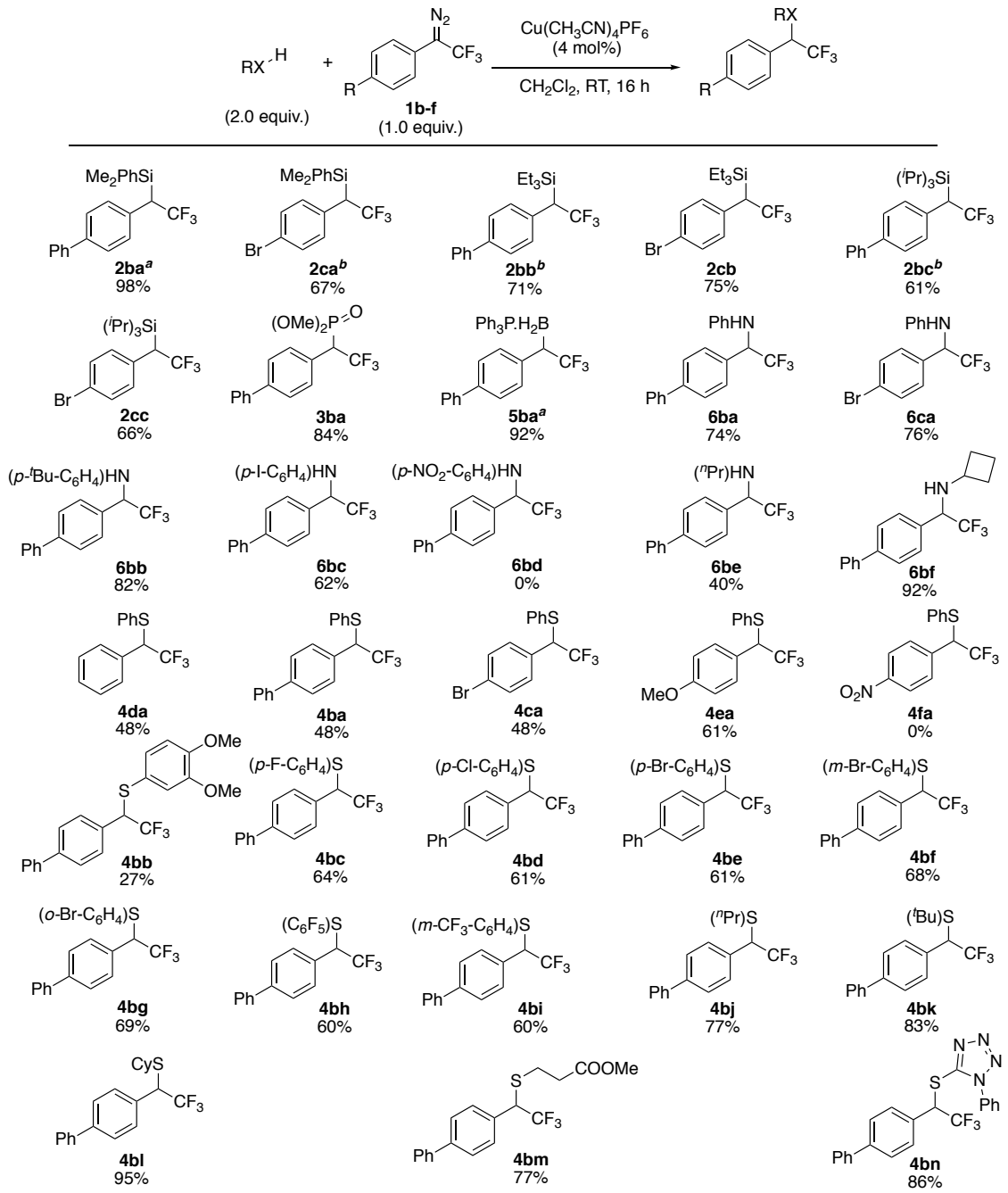


Scheme 2.7 Synthesis of diazo compounds.

The reactivity of 1-aryl-2,2,2-trifluoro-1-diazoethanes **1b-f** was probed against a range of substrates for heteroatom-hydrogen insertion; pleasingly, insertion with these less reactive donor/acceptor diazo compounds was successful, and demonstrates the first example of XHI with α-substituted trifluorodiazoethanes (**Scheme 2.8**). For these donor/acceptor diazo compounds, the reaction was performed with an excess of the substrate, and the catalyst loading typically increased to 4 mol% to push the reaction to completion. Furthermore, upon completion of the addition of the diazo compound with a syringe pump, the orange colour – characteristic of the diazo compound – persisted, showing only minimal signs of dimerisation, unlike unsubstituted 2,2,2-trifluorodiazoethane **1a**. Therefore, the reaction was left to stir until complete conversion was achieved – typically up to 16 h. As with insertion with 2,2,2-trifluorodiazoethane **1a**, the generality of the reaction is exceptional, with this system successfully achieving insertion into the same five heteroatom-hydrogen bond types: Si-H, P-H, S-H, B-H, and N-H. A detailed investigation of S-H insertion reactions revealed that aryl, heteroaryl, primary, secondary, and tertiary alkyl groups are all tolerated on the sulfur atom. Variation of the diazo compound was also tolerated, with

the notable exception of electron deficient diazo compounds; for example, the *para*-methoxy substrate **4ea** was readily formed in 61 % yield whereas the *para*-nitro variant **4fa** did not form at all – instead only dimerization of the diazo starting material was observed. This is consistent with previous reports that donor/acceptor carbenoids are more stable than highly electron deficient acceptor/acceptor carbenoids, which are prone to rapid dimerization.[266] In contrast to the product outcome observed with 2,2,2-trifluoro-1-diazoethane **1a**, aniline derivatives underwent monoinsertion, with no detectable products resulting from undesired double insertion. Primary alkyl and cycloalkyl amines also reacted with α-substituted trifluorodiazoethanes **1b-f** as demonstrated with the synthesis of **6be** and **6bf**, which were isolated in 40 % and 92 % yield, respectively.

Compounds **2ba** and **5ba** synthesised by Dr. Benoît Liégault. Compounds **2ca**, **2bb** and **2bc** synthesised by Dr. Janis Veliks.



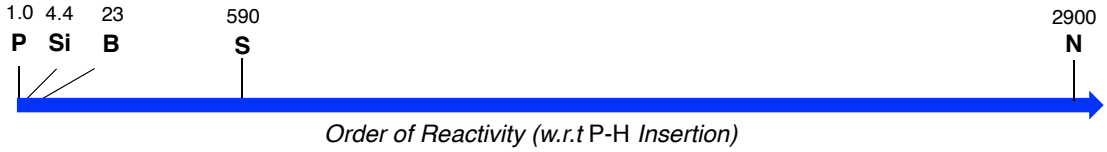
Scheme 2.8 Scope of XHI with α-aryl-2,2,2-trifluorodiazoethanes. Yields given are for the isolated product. [*a*] Compound synthesised by Dr. Benoît Liégault. [*b*] Compound synthesised by Dr. Janis Veliks.

2.3.2 Order of Reactivity

Competition experiments performed by Dr. Janis Veliks.

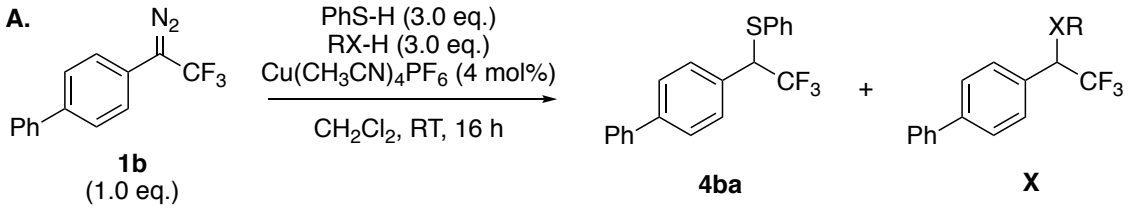
The ability of $[Cu(CH_3CN)_4]PF_6$ to efficiently catalyse a range of XHI reactions led us to carry out a series of competition experiments, with the diazo compound **1b,** to provide an order of reactivity: N-H > S-H > B-H > Si-H > P-H (**Table 2.2**). Interestingly, aryl thiols reacted faster than alkyl thiols, and the reaction slows down upon going from primary to secondary to tertiary alkyl thiols (**entries 2 – 4**). This may result from the increasing S-H bond dissociation energies going from benzenethiol (349 $kJmol^{-1}$), to propanethiol (366 $kJmol^{-1}$), to cyclohexyl thiol (370 $kJmol^{-1}$), to *tert*-butylthiol (371 $kJmol^{-1}$).[294]

Placing the substrate classes in order of reactivity (with respect to P-H insertion) reveals that N-H insertion is 2900 times faster than P-H insertion, S-H insertion is 590 times faster, and B-H and Si-H insertion are comparable to P-H insertion (**Scheme 2.9**).

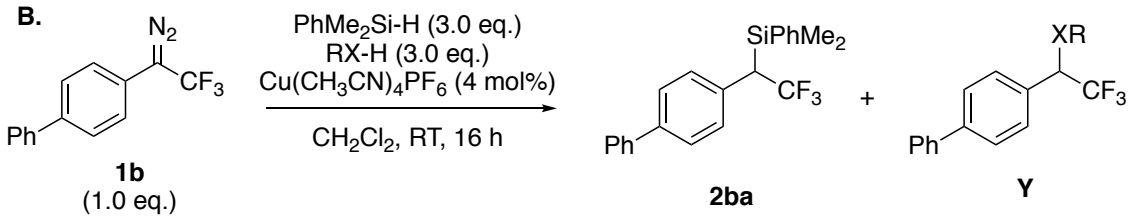


Scheme 2.9 Order of reactivity of XHI substrate classes.

Table 2.2 Competition Experiments



Entry	RX-H	X	Ratio 4ba : X
1	$PhNH_2$	**6ba**	1 : 4.8
2	^{n}PrSH	**4bj**	1 : 0.5
3	CySH	**4bl**	1 : 0.3
4	^{t}BuSH	**4bk**	1 : 0.2
5	$Ph_3P.BH_3$	**5ba**	1 : 0.05
6	Me_2PhSiH	**2ba**	1 : 0.0
7	(MeO)P(O)H	**3ba**	1 : 0.0



Entry	RX-H	Y	Ratio 2ba : Y
8	$Ph_3P{\cdot}BH_3$	**5ba**	1 : 5.1
9	$(MeO)_2P(O)$-H	**3ba**	1 : 0.23

Cy = cyclohexyl. A) Copper-catalysed Si-H, B-H, P-H, and N-H insertion versus PhS-H insertion with **1b**, and copper-catalysed B-H and N-H insertion versus Si-H insertion with **1b**. The product ratio was determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as internal reference.

Separating the substrates according to their mechanistic profile – stepwise or concerted – allows for a more informative assessment of these results. For lone-pair bearing substrates, the rate determining step for Cu(I)-carbenoid insertion has been shown to be attack of the heteroatom on the carbenoid, with the other steps – coordination of the diazo compound to the metal, nitrogen extrusion, and collapse of the ylide – all having similar transition state energies.[295] Amines appear to attack the carbene intermediate faster than thiols in this system. This trend was also

observed by Woo and co-workers in their comparison of amine and thiol substrates in Iridium(III)-catalysed XHI reactions with diazoacetates.[296]

The relative rates of reaction for substrates bearing no lone pairs, B-H, Si-H and P-H (**Table 2.2b**), may be rationalised by each substrate's ability to stabilise the partial positive charge that accumulates on the heteroatom during the concerted mechanism. Triphenlylphosphine protected borane complex contains an electron donating triphenylphosphine ligand capable of such stabilisation and hence reacts fastest. Dimethyl phosphite reacts slowest as the P=O bond is highly ionic, with a significant partial positive charge already on the phosphorous prior to insertion – some studies suggest that the phosphosous-oxygen bond in phosphine oxides is a dative bond and better represented in a similar fashion to amine oxides, R_3P^+-O^-.[297] Dimethylphenylsilane is neither destabilised nor possessing electron-donating ligands and hence lies between the other two substrates.

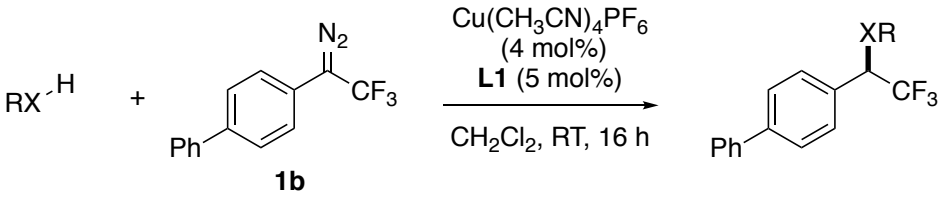
This ability of substituents effecting the rate of the reaction for XHI reactions that proceed *via* concerted mechanisms is well documented within the literature – this phenomenon has been exploited to direct the regioselectivity of C-H insertion.[266,285]

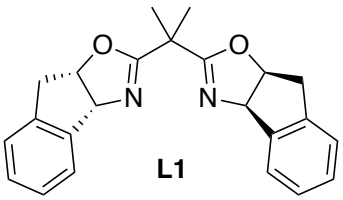
2.4 Asymmetric XHI with α-Substituted Trifluorodiazoethanes

2.4.1 Asymmetric B-H Insertion

The presence of a stereocentre in these XHI products prompted a study into the development of an asymmetric variant of the reaction. Given the high prevalence of copper-bisoxazoline ligand-based systems for asymmetric cyclopropanation and insertion reactions with α-diazocarbonyl compounds,[298] initial screening was focused on the bisoxazoline (BOX) ligand scaffold, starting with ligand **L1** (**Table 2.4**).

Table 2.4 Screening of ligand **L1** for Asymmetric XHI.



Entry	ligand	Substrate	Yield/ %	e.e./ %
1		PhHN–H	62	0
2		PhS–H	53	0
3		$(MeO)_2(O)P$–H	21	0
4		$Ph_3P{\cdot}H_2B$–H	74	42
5 [a]		$Ph_3P{\cdot}H_2B$–H	80	59

L1

$Cu(CH_3CN)_4PF_6$ (4 mol%) and the chiral ligand (5 mol%) were placed into a vial. CH_2Cl_2 (0.5 mL) was added and the solution stirred at room temperature for 2 h. The substrate (2 equiv.) was then added, followed by a solution of the **1b** (1 equiv.) in CH_2Cl_2 (0.7 mL) over 1 hour with a syringe pump. Once the reaction was complete, the solvent was evaporated and the crude product directly loaded onto a silica gel chromatography column for purification. The enantiomeric excess of purified product was determined using chiral HPLC. [*a*] Addition of 5 mol% of $NaBAr_F$.

For the fastest reacting substrate classes, N-H and S-H, no enantioinduction was observed (entries **1** and **2**). The low level of enantiocontrol observed in S-H insertion reaction may be attributed to two factors: the high coordination ability of the sulfur atom to the transition metal may destroy the active chiral catalyst;[288] secondly, the relatively high

stability of sulfonium ylide may facilitate the degeneration of metal-associated ylide to free ylide, which lowers the efficiency of chiral induction of the catalyst.[288] Therefore, the catalytic asymmetric S-H insertion reaction is a challenge. A similar lack of selectivity was also observed with P-H insertion (entry **3**). However, when **L1** was tested against triphenylphosphine-protected borane, the enantioenriched B-H insertion product was observed in 74 % yield and 42 % *e.e* (entry **4**). This could be improved slightly by addition of the larger, non-coordinating ion $^{-}BAr_F$ (entry **5**). $NaBAr_F$ (**Figure 2.12**) has been successfully applied in a range of catalytic asymmetric transformations for modifying the reactivity and enantioselectivity of catalysts, including the enantioselective insertion of carbenoids into N-H bonds.[299]

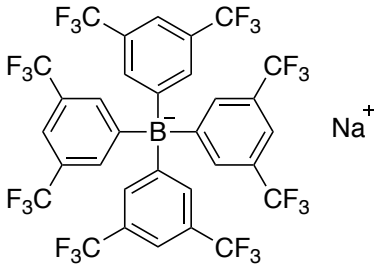
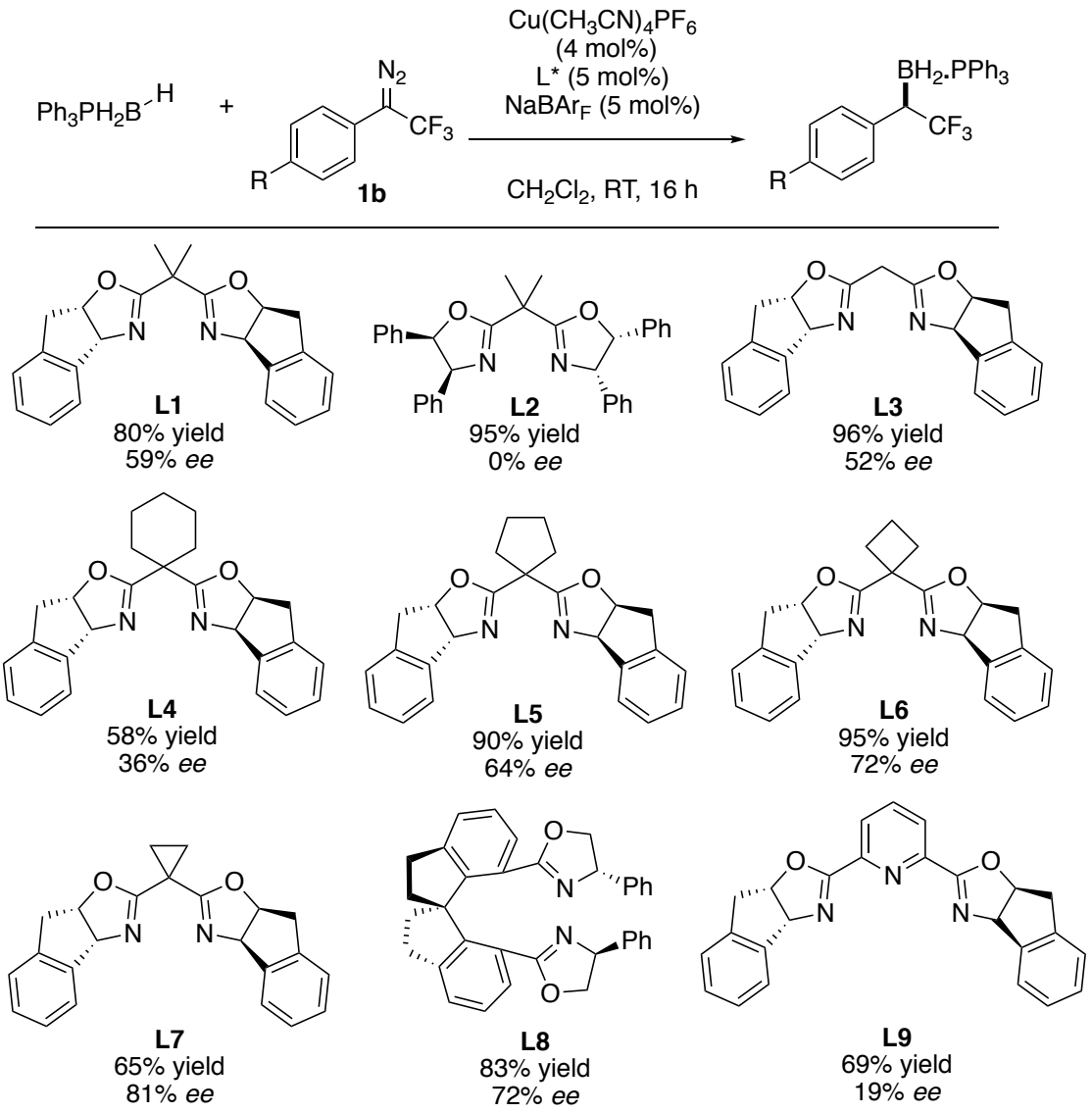


Figure 2.12 Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$).

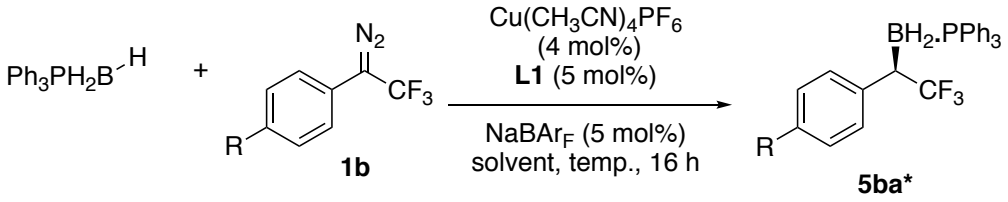
This encouraging result prompted a study into the ligand design (**Scheme 2.10**). Removal of the rigid indane wings proved detrimental to selectivity (**L2**), and so the substitution on the methylene bridge was explored instead: decreasing the ring size – and thereby increasing the N···N bite angle, θ – increased selectivity (ligands **L3 – L7**), although a limit was reached with the cyclopropyl ligand. Neither Spiro-BOX ligand **L8** or pyBOX ligand **L9** performed as well as **L7**.



Scheme 2.10 Ligand screen for asymmetric B-H insertion.

Neither changing the solvent nor running the reaction at lower temperature improved selectivity (**Table 2.5**).

Table 2.5 Screening of Conditions for Asymmetric B-H Insertion.

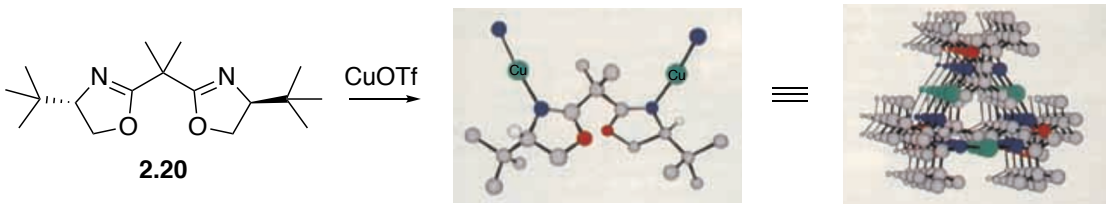


Entry	Solvent	Temperature/ °C	Yield/ %	*e.e.*/ %
1	CH_2Cl_2	25	65	81
2	toluene	25	38	71
3	CH_2Cl_2	-35	69	70

$Cu(CH_3CN)_4PF_6$ (4 mol%), $NaBAr_F$ (5 mol%) and the chiral ligand (5 mol%) were placed into a vial. Solvent was added and the solution stirred at room temperature for 2 h. The substrate (2 equiv.) was then added, and the solution set to the correct temperature followed by a solution of **1b** (1 equiv.) in the desired solvent over 1 hour with a syringe pump. Once the reaction was complete, the solvent was evaporated and the crude product directly loaded onto a silica gel chromatography column for purification. The enantiomeric excess of purified product was determined using chiral HPLC.

This positive correlation between enantioselectivity and bite angle θ is consistent with the work of Davies and co-workers; they found that enantioselectivity of the copper(II)-bisoxazoline catalysed Diels-Alder reaction could be increased by increasing the bite angle, θ. This is thought to arise from an increase in bite angle resulting in a change in the orientation of the C_8-H proton in the 'chiral pocket'.[300] However, Müller and co-workers found the opposite – that enantioselectivity of the copper(I)-BOX catalysed intramolecular carbenoid insertion into C-H bonds decreased with an increase in bite angle.[301] This decrease in enantioselectivity with bite angle was also observed by Jørgensen and co-workers in a copper(I)-BOX catalysed intermolecular carbenoid insertion into N-H bonds.[302] Seemingly optimal ligand selection is highly substrate dependant, and highly selective systems may not necessarily translate to other transformations.

The structure of copper (I)-BOX complexes are unusual – Evans and co-workers showed that these C_2-symmetrical ligands form chiral, non-racemic, helical coordination polymers (**Figure 2.13**). X-ray crystal structures of **2.20** show a single-stranded helical polymer with threefold symmetry, where the bisoxazoline ligand occupies a bridging position between two nearly linear, two-coordinate copper (I) ions. The ligand adopts a conformation wherein the bulky groups – in this example large *tert*-butyl groups – are directed away from the centre of the helix. Accordingly, the C_2-symmetric bisoxazoline ligand, due to its chirality, directs both the assembly of the polymer and the sense of helicity. The Cu···N bond lengths (1.88 Å) are typical for two-coordinate copper(I) species.[303] Later, Šunjić and co-workers demonstrated from UV, NMR and CD spectroscopy that the most stable ratio of copper (I) to ligand is 1:1, consistent with Evans' work.[304]



2.20

Figure 2.13 Structure of copper (I)-BOX complexes. Used with permission from Angewandte Chemie International Edition.

The bisoxazoline-based ligands were synthesised by Dr. Janis Veliks according to disclosed procedures: commercially available chiral β-amino alcohols were condensed with dinitriles using stoichiometric amount of zinc (II) triflate (**Figure 2.14**).[305,306] For **L4**, **L5** and **L6** the cycloalkyl dinitrile intermediates were synthesised by double substitution of the corresponding dihaloalkane by malononitrile **A**.[307] For **L1** and **L2**, dimethylmalononitrile is commercially available. **L3**, **L8** and **L9** are commercially

available; **L7** was made from **L3** by double nucleophilic substitution of 1,2-dibromoethane **C**.[308]

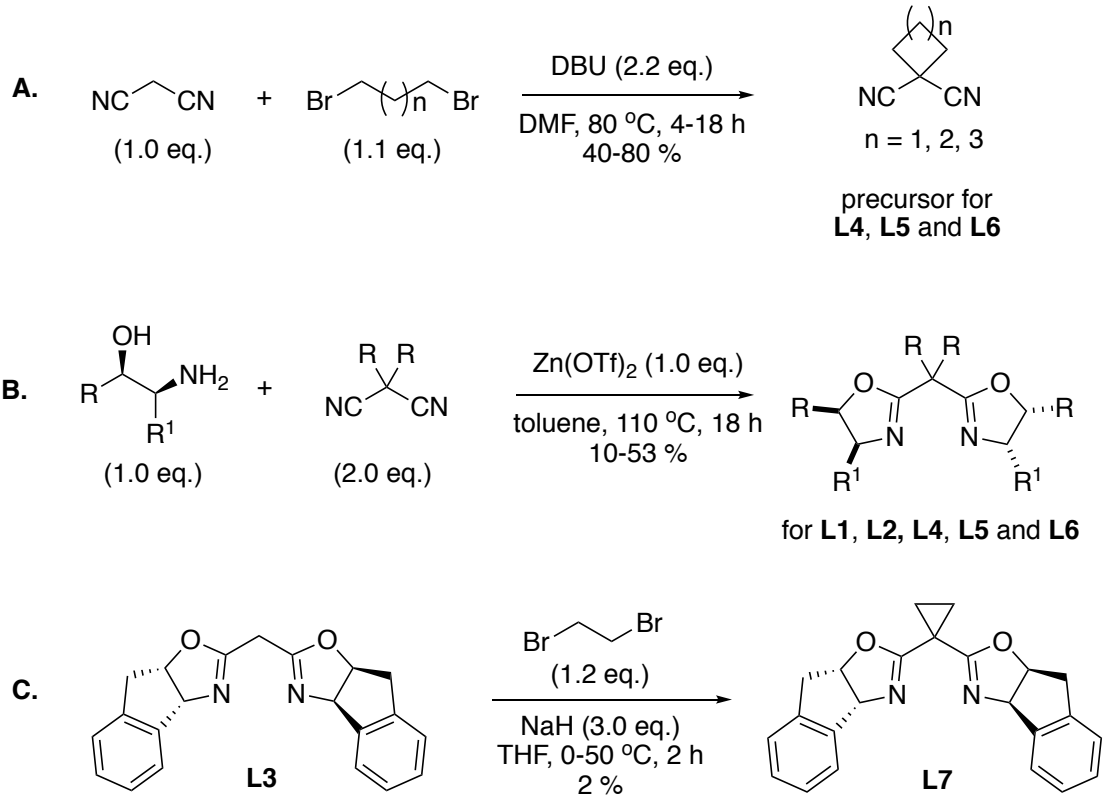
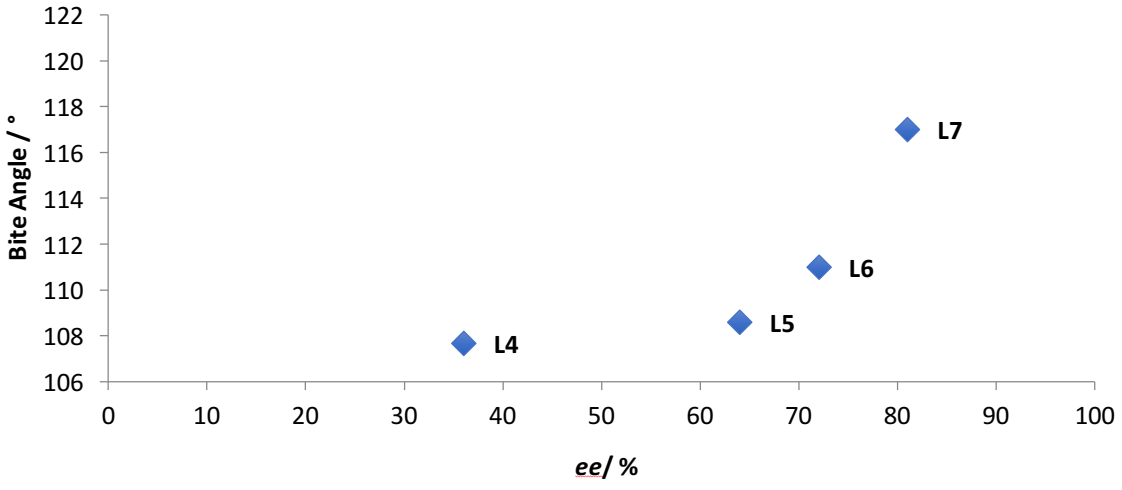


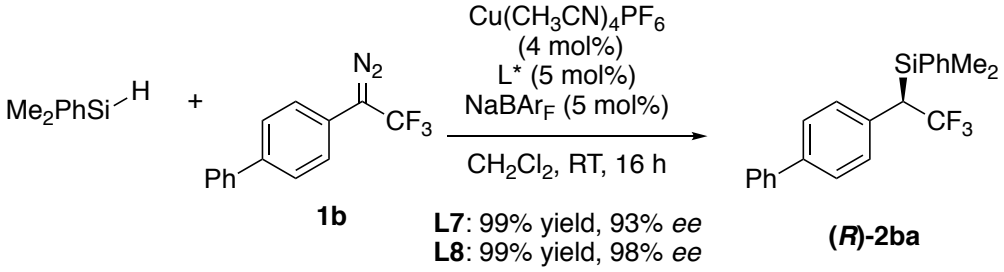
Figure 2.14 Synthesis of chiral bisoxazoline-based ligands. Ligands synthesised by Dr. Janis Veliks.

Graph 2.1 *e.e.* of B-H Insertion product **5ba** verses N···N bite angle of Ligand.[300]



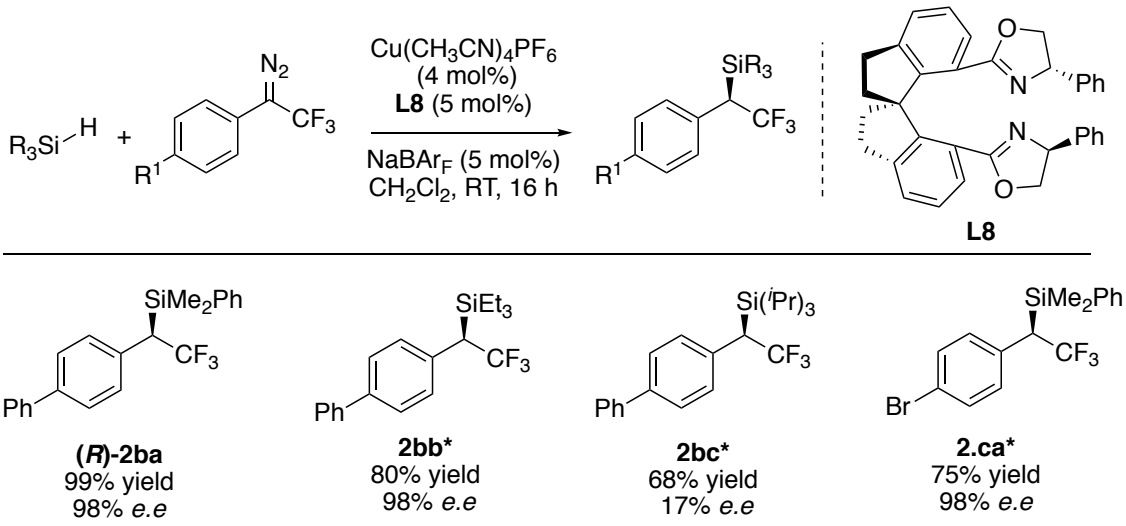
2.4.2 Asymmetric Si-H Insertion

As represented in **graph 2.1**, a limit was reached for enantioselective installation of the α-branched trifluoroethyl unit into triphenylphosphine-protected borane. Hence, the best two ligands for B-H insertion, **L7** and **L8**, were probed for asymmetric XHI with the final substrate class – silanes. Pleasingly both **L7** and **L8** furnished the desired Si-H insertion product **2ba** in quantitative yield and with excellent selectivity – 93 % *e.e.* for **L7** and 98 % *e.e.* for **L8** (**Scheme 2.11**).



Scheme 2.11 Asymmetric Si-H Insertion Ligand screen.

Modifying the diazo compound was tolerated for the reaction, as was variation of the silane (**Scheme 2.12**) – however, increasing the steric bulk of the substituents on the silane was detrimental to both yield and selectivity.



Scheme 2.12 Scope of Asymmetric Si-H Insertion.

L8, developed by Zhou and co-workers, has been tested against XHI with α-diazoesters by the same group.[288] Gillingham and co-workers looked at the minimized 3D structures of the ligand, and the conformation that would be required for bidentate chelation with copper(I). In the minimal energy conformer (**Figure 2.15, left**) the nitrogens prefer to be more than 6 Å apart, precluding bidentate chelation. In the rotamer that would be required for copper chelation there is only 3.0 Å between the two nitrogens (**Figure 2.15, right**). Based on typical Cu-N bond lengths in similar complexes, this space would be too small for copper coordination. With less rigid ligands, a simple conformational adjustment would readily occur to accommodate metal binding, but the rigid spiro-motif in these ligands prohibits this possibility.[283]

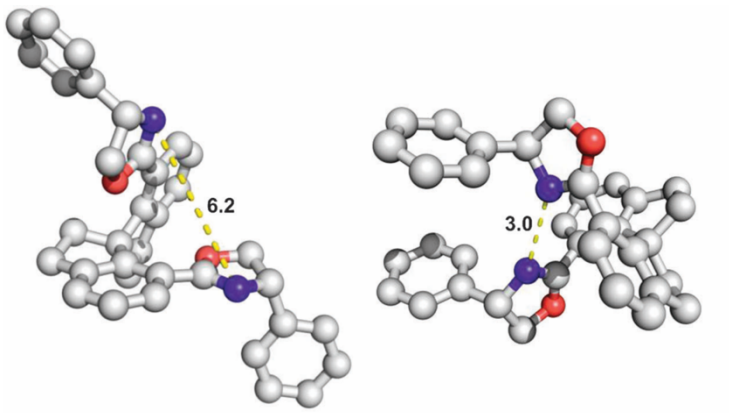


Figure 2.15 Left: lowest energy conformer of Zhou ligand (MM2 minimisation). Right: oxazole rotamers that would be required for bidentate chelation to copper. Used with permission from Royal Society of Chemistry.

Zhou and co-workers proposed an explanation for this peculiarity; through crystal structures of Cu(I)-(*Sa*,*S*,*S*)-**L8** with $BArF^-$ counterion, they observed an unexpected binuclear structure – with two copper(I) atoms being coordinated by two nitrogen atoms from the two spiro-bisoxazoline ligands (**Figure 2.16**). The N1-Cu1-N3 and N2-Cu2-N4 angles are 169.0(2)° and 169.5(2)°, respectively, which means that the two nitrogen

atoms coordinate to a copper(I) atom in a trans orientation. The phenyl groups of the oxazoline ligands form a perfect C_2-symmetric chiral pocket around the copper centre. The copper atoms in this complex have a 14-electron structure, with the distance between the two copper centres being 2.7828(10) Å. This dimeric species was also observed by electrospray ionization mass spectrometry (ESI-MS). Furthermore, a small but clearly positive non-linear effect was observed in the Cu(I)-(*Sa*,*S*,*S*)-**L8-**catalyzed N-H insertion reaction, indicating that the dimeric copper complex is most likely the real active catalyst for the N-H insertion reaction.[288]

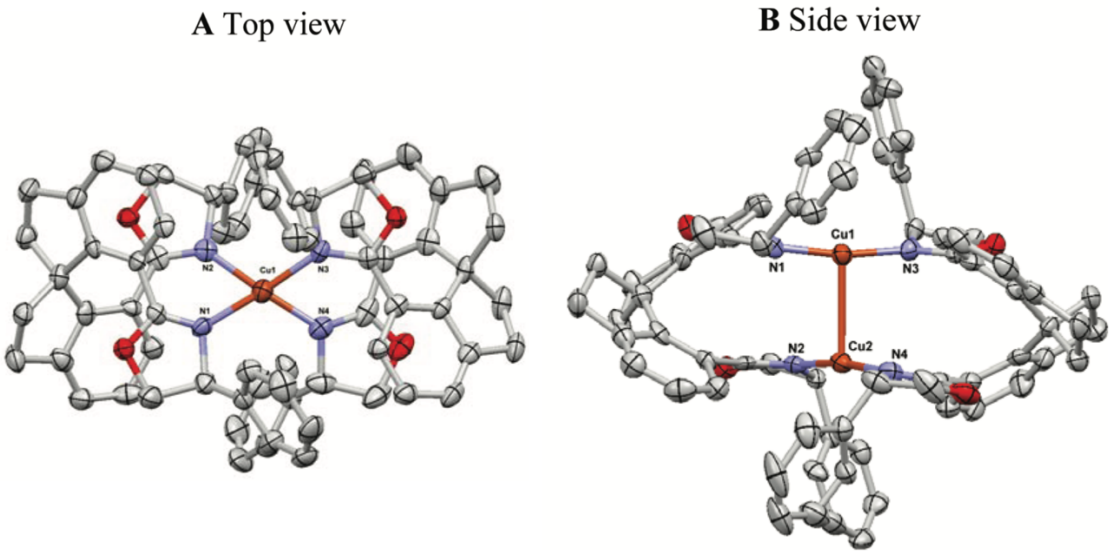
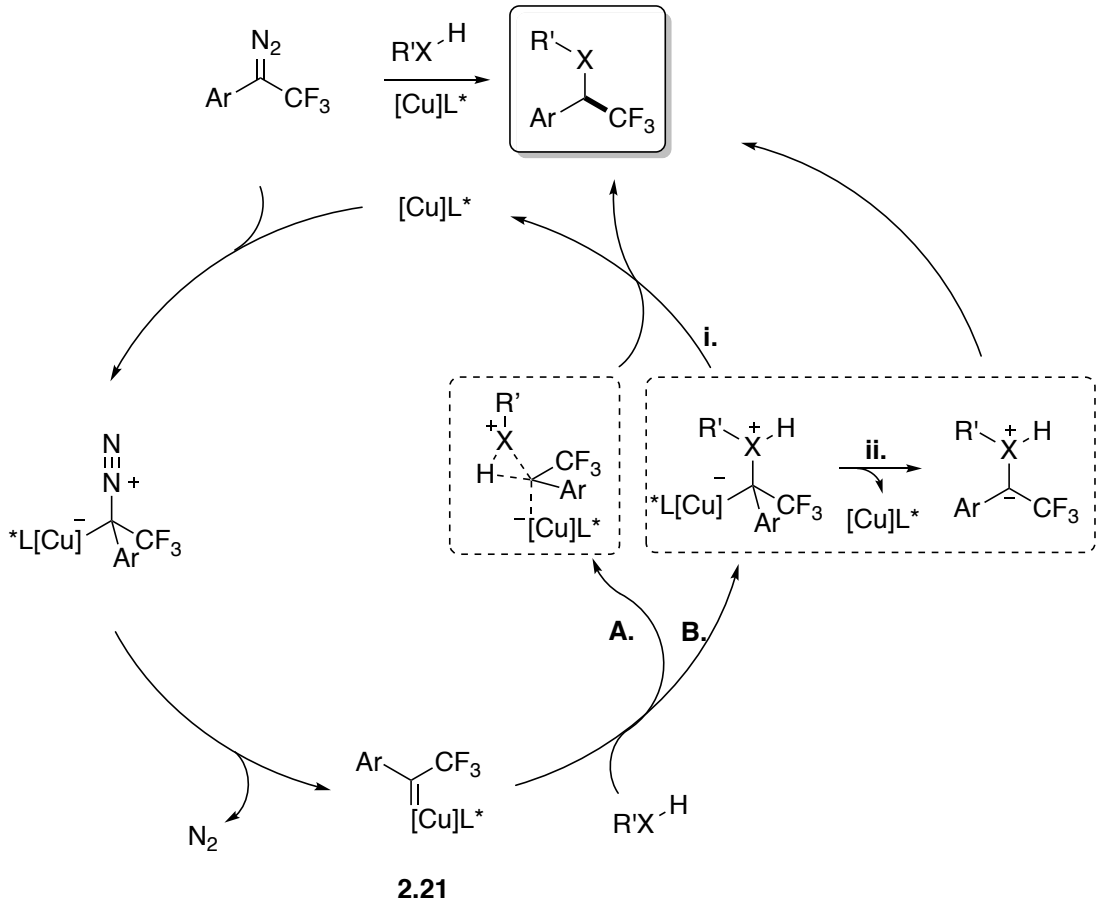


Figure 2.16 Single crystal structure of Cu(I)-(*Sa*,*S*,*S*)-**L8** complex. Reprinted with permission from American Chemical Society. Copyright 2012.

2.4.3 Mechanistic Considerations

The fact that this system induced enantioselectivity for silicon- and boron-based substrates – and not for nitrogen-, sulfur- and phosphorous-based substrates – may be explained based upon a mechanistic consideration (**Scheme 2.13**). Specifically, the pathway from carbenoid **2.21** to product is of paramount importance when discussing stereoselectivity of XHI reactions. It is generally accepted that a concerted pathway **A** is favoured for heteroatoms bearing no lone pair of electrons.[283,288] Following this pathway allows for facile transfer of chiral information to the final product, and explains why enantioinduction was observed for Si-H and B-H insertion.

Regarding substrates with lone pairs on the heteroatom – in this case amines and thiols – an ylide pathway **B**, is generally accepted. Here, the first step is attack of the nucleophilic substrate to form the copper-associated ylide, which may collapse *via* one of two routes to release the XHI product and regenerate the catalyst. In pathway **B.i.,** proton transfer occurs simultaneously with catalyst dissociation from a metal-bound ylide; because the chiral catalyst is involved in the product forming step, chiral induction can be expected. The alternative process, **B.ii.,** involves dissociation of the copper catalyst to form free ylide, which then undergoes a proton transfer to yield the insertion product; because the chiral catalyst does not participate in the final product forming step, enantioselectivity is not observed.[283,288]



Scheme 2.13 Catalytic cycle of XHI reactions with α-substituted trifluorodiazoethane.

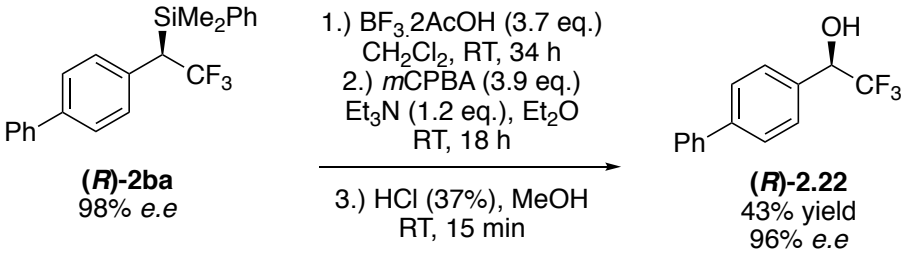
The above argument satisfactorily explains the observed stereoselectivity of α-aryl trifluorodiazoethane insertion with various substrates – however, under very similar conditions, Zhou and co-workers successfully achieved asymmetric N-H[299] and S-H[309] insertion with α-aryl diazoesters. This indicates that substitution of an ester functionality with a trifluoromethyl group has a significant effect on selectivity, and by extension the mechanism of the reaction. Presumably, this is due to increased electron withdrawing capability of the trifluoromethyl group offering increased stabilisation of the free ylide, and so favouring pathway **B.ii.** Zhou and co-workers found that the enantiomeric ratio of N-H insertion reactions decreased linearly upon iteratively increasing the electron withdrawing capability of the diazo unit – a consequence of stabilisation of the free ylide

and therefore favouring pathway **B.ii**. Similarly, they demonstrated that increasing the electron donating capability of the XHI substrate decreases the enantiomeric ratio – again by favouring pathway **B.ii** through stabilising the ylide.[288] These results give weight to this mechanistic model for heteroatoms bearing a lone pair.

The electron withdrawing capability of the trifluoromethyl group is only slightly greater than that of the ethyl ester group: CF_3 (σ_{meta} = 0.43 and σ_{para} = 0.54) and CO_2Et (σ_{meta} = 0.37 and σ_{para} = 0.45).[310] This suggests that only a slight change in the electronics of the diazo compound can alter the pathway for the reaction and thus impact stereoselectivity.

2.4.4 Determination of absolute stereochemistry

The products resulting from Si-H insertion are oils, and so determination of absolute stereochemistry by X-ray crystallography was not feasible. However, product **2ba** was identified as a substrate with potential to undergo a stereoretentive Tamao-Fleming oxidation.[311] The aforementioned reaction was performed, yielding the resulting known alcohol **2.22;** the *e.e.* of which was determined by HPLC to be > 96 %. By comparing the $[\alpha]_D$ value of the resulting enantiomerically enriched alcohol **(*R*)-2.22** (*e.e.* > 96 %) with a previously reported value, the configuration of **2ba** could be assigned as *R* (**Scheme 2.14**).[312]



Scheme 2.14 Stereoretentive Tamao-Fleming Oxidation for Determination of Absolute Stereochemistry.

2.4.5 Summary of Cu-Catalysed XHI

The copper(I)-catalysed XHI reaction described above offers a significant contribution to synthetic methodology for accessing the heteroatom-trifluoroethyl motif, in non-substituted, α-substituted and asymmetric modes.

The procedure offers significant advantages to previously disclosed methods based on the following criteria: operationally simple – no need to distil **1a**; operationally safe – no need to handle neat **1a**; applicable to a broad range of substrates – five heteroatom-hydrogen bond types: Si-H, P-H, S-H, B-H, and N-H; reasonable stoichiometry – 2.3 equivalents is the maximum of any reactant compared with the limiting reagent; catalyst and ligand loading are <4 mol% and 5 mol% respectively, and both are commercially available; acceptable reaction times – as low as 30 minutes; broadly good yields – up to 99 %; and excellent enantioselectivity for silane insertion – up to 98 % *e.e.* However, neither C-H or O-H insertion was observed under the reaction conditions.

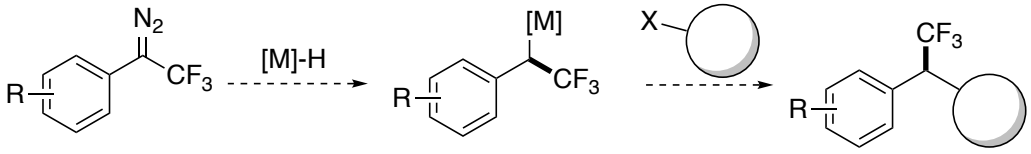
The ability of a single system to catalyse a single transformation in such a broad range of substrate classes demonstrates the robustness, and broad applicability of this reaction.

However, asymmetric variants of this transformation are only possible with two of the substrate classes – limiting its general applicability. Furthermore, comparing the observed lack of selectivity for N-H insertion with trifluoromethyl diazo compounds and the successful, literature-reported N-H insertion with diazo carbonyl compounds, it is apparent that such a subtle change as replacement of an ester with a trifluoromethyl functionality on the diazo component can change the stereochemical outcome of the reaction.

2.5 Rhodium-Catalysed XHI into Tin-Hydrogen Bonds

2.5.1 Introduction

Next, it was decided to target insertion into metal hydrides; such a reaction would yield products capable of undergoing transition-metal catalysis to install branched trifluoroethyl groups onto a range of coupling partners. This was the driving motivation of the second part of this chapter (**Scheme 2.15**).



Scheme 2.15 Proposed Metal-Hydride insertion and Subsequent Coupling Reaction.

The first metal hydride targeted for insertion was tin hydride, as the resulting product of such a XHI reaction – organnostannanes – could be tested for Stille-type cross coupling reactions.[313] Methods to access 2,2,2-trifluoroethylstannanes are limited to two disconnections; radical recombination resulting from the photolysis of hexafluoroacetone and tetramethylstannane (**A**),[236] and carbene insertion into the Sn-H bond (**B**) (**Figure 2.17**).[237]

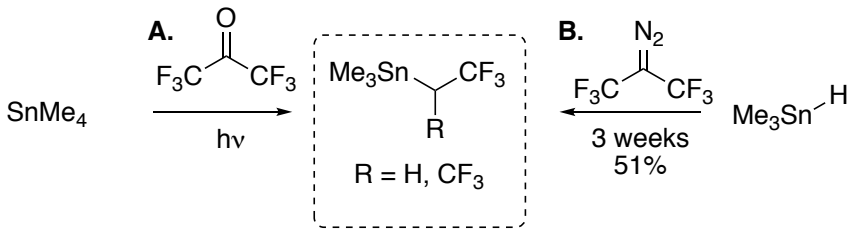


Figure 2.17 Reported syntheses of 2,2,2-trifluoroethylstannanes.

Trialkyltin hydride insertion has been little studied, despite several early reports from Michael Doyle and co-workers supporting the feasibility of such an insertion with carbenes (**Figure 2.18)**. These first examples of Sn-H XHI utilise diazirines to generate the carbene, and require long reaction times (up to three days)[314] or use of toxic conditions **A** (refluxing in benzene).[315,316] The first example of Sn-H XHI utilising a diazo compound was by Cullen and Waldman who achieved Sn-H insertion with bis(trifluoromethyl)diazomethane. However, this uncatalysed reaction took three weeks to reach completion, and required fractional distillation to isolate the XHI product in modest yield. Furthermore, this procedure does not offer a platform to access enantioenriched products as the products are achiral **B**.[237] In 1995, Landais reported the first example of transition-metal-catalysed trialkyltin hydride insertion with diazo esters, using rhodium(II) acetate **C**.[317] More recently, Bi and co-workers disclosed a successful method for insertion into the Sn-H bond using AgOTf as catalyst, with the diazo compound generated *in situ* from *N*-nosylhydrazones **D**.[232] Finally, in 2017, Jianbo Wang and co-workers disclosed a transition-metal-free carbene XHI reaction into trialkyltin hydrides; they also generate the diazo compound *in situ*, from *N*-tosylhydrazones **E**.[318] Notably, none of these methods offer a route to asymmetric Sn-H insertion.

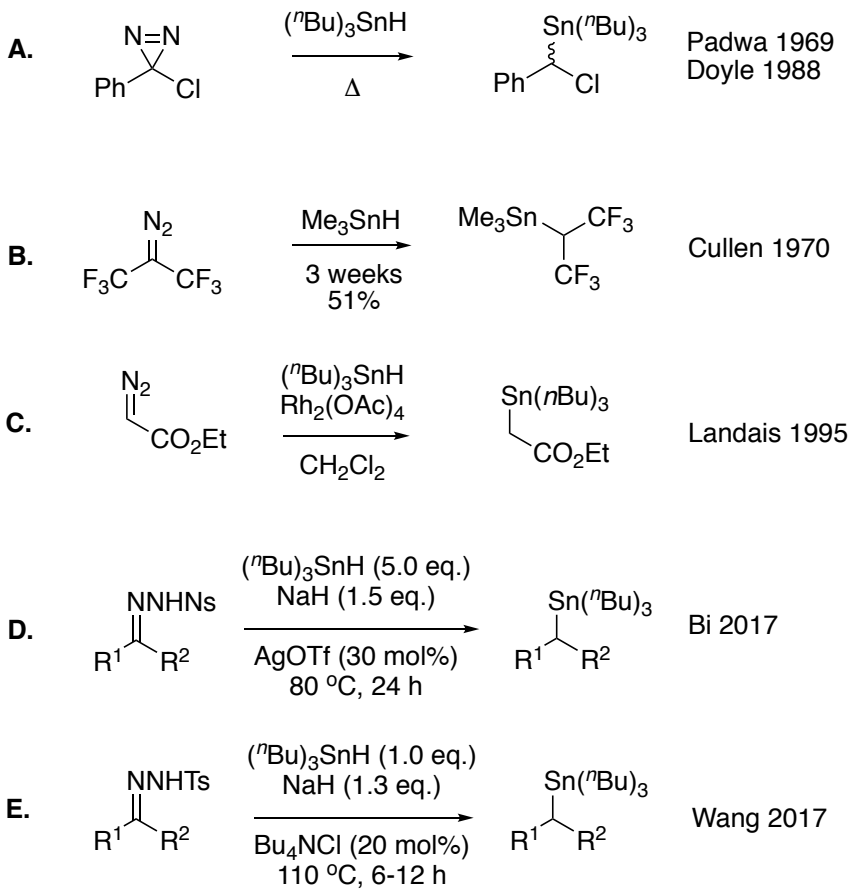


Figure 2.18 Reported Sn-H insertion reactions.

Wang also showed that tributyltin hydride facilitates reduction of diazo compounds to the corresponding CH_2 products *via* protodestannylation of the tin hydride insertion intermediate (**Figure 2.19**).[319]

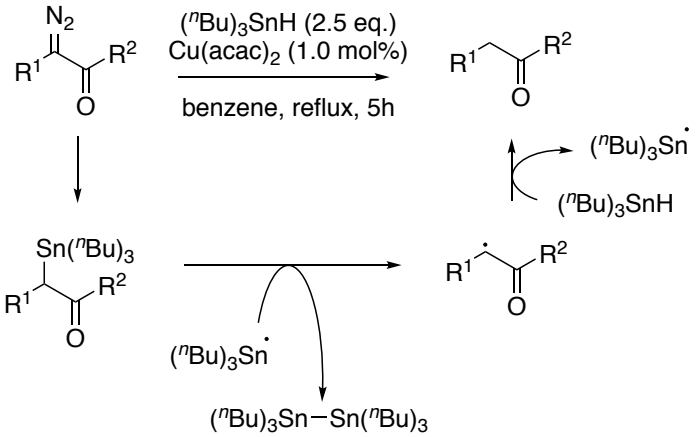
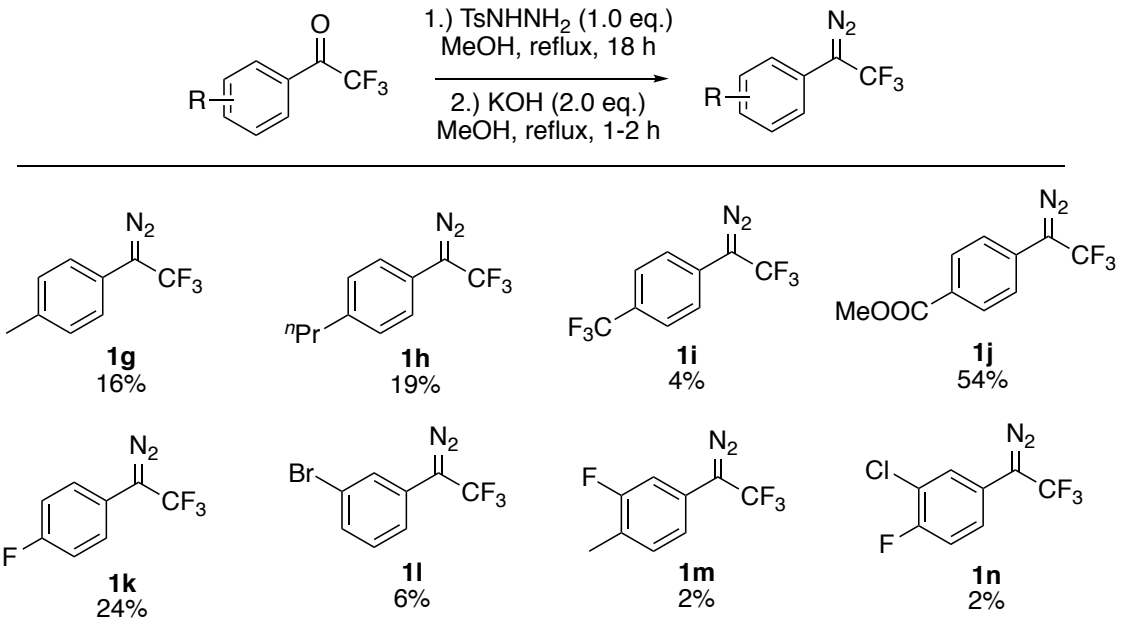


Figure 2.19 Protodestannylation of Sn-H insertion product.

2.5.2 Reaction Development

The starting materials for this study – aryl-substituted 2,2,2-trifluorodiazoethanes – were prepared according to previously reported literature procedures (**Scheme 2.16**).[269,273,275,279] Synthesis of diazo compounds **1b**-**1f** are reported in **Scheme 2.7**.

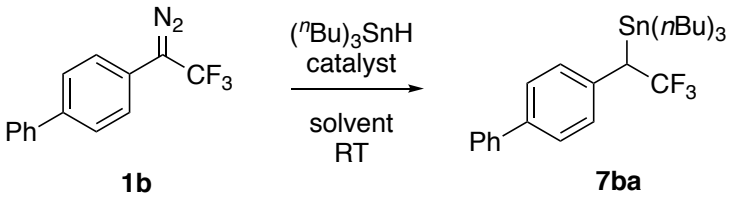


Scheme 2.16 Synthesis of diazo compounds.

Preliminary studies into tributyltin hydride insertion were performed using 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl **1b** as the model substrate (**Table 2.5**). When employing the previously developed conditions – slow addition of diazo compound **1b** to a mixture of $Cu(MeCN)_4PF_6$ and substrate – low yield of the desired product **7ba** was obtained, in addition to a significant amount of reduction product (**entry 1**). Neither decreasing the amount of $(^nBu)_3SnH$ to 1.0 equivalent or changing the order of addition were beneficial (**entries 2 to 4**). $Rh_2(OAc)_4$ catalyst gave comparably poor results (**entry 5**) with those obtained with the copper catalyst following the same procedure. However, when the $Rh_2(OAc)_4$ catalyst was added in one portion to an equimolar mixture of diazo

compound **1b** and (^{n}Bu)$_3$SnH in dichloromethane in an open vial, instantaneous evolution of nitrogen and disappearance of characteristic orange colour of diazo compound was observed (**entry 6**). The desired insertion product **7ba** was isolated in 64% yield. Cu(II) and Rh(I) were ineffective for this transformation (**entries 7 and 8**). Screening various solvents highlighted CH_2Cl_2 as an optimum solvent for this transformation (**entry 5 vs. entries 9-12**). When a reagent mixture of (^{n}Bu)$_3$SnH and diazo compound **1b** was quickly transferred to a suspension of catalyst the yield of the desired product **7ba** was further improved (**entry 13**). Finally, probing catalyst loading identified 4 mol% of $Rh_2(OAc)_4$ as an optimal condition for this transformation (**entry 13 vs. 14 and 15**). Thus, the final reaction conditions consisted of addition of an equimolar solution of **1b** and (^{n}Bu)$_3$SnH in CH_2Cl_2 to a suspension of $Rh_2(OAc)_4$ at room temperature.

Table 2.5 Optimisation of Rhodium Catalysed XHI into Tin Hydrogen Bonds.[a]



1b **7ba**

Entry	Catalyst	Solvent	Procedure[c]	Yield/ %[d]
1[b]	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**A**	25
2	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**A**	26
3	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**B**	4
4	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**C**	traces
5	$Rh_2(OAc)_4$	CH_2Cl_2	**A**	25
6	$Rh_2(OAc)_4$	CH_2Cl_2	**C**	64
7	$Cu(OAc)_2$	CH_2Cl_2	**C**	traces
8	$Rh(PPh)_3Cl$	CH_2Cl_2	**C**	(6)
9	$Rh_2(OAc)_4$	$CHCl_3$	**C**	(43)
10	$Rh_2(OAc)_4$	Toluene	**C**	(59)
11	$Rh_2(OAc)_4$	Hexane	**C**	(43)
12	$Rh_2(OAc)_4$	DCE	**C**	(45)
13	**$Rh_2(OAc)_4$**	**CH_2Cl_2**	**D**	**74**
14	$Rh_2(OAc)_4$[e]	CH_2Cl_2	**D**	67
15	$Rh_2(OAc)_4$[f]	CH_2Cl_2	**D**	74

[a] All reactions performed on a 0.1 mmol scale with 1.0 eq. of **1b** and $(^nBu)_3SnH$, with 4.0 mol% catalyst loading, unless stated otherwise**.** [b] 2.0 eq. of $(^nBu)_3SnH$. [c] **Procedure A:** Syringe pump addition of **1b** solution to a mixture of cat. and $(^nBu)_3SnH$ in CH_2Cl_2 over 1h. **Procedure B:** Syringe pump addition of **1b** and $(^nBu)_3SnH$ solution to a catalyst suspension in CH_2Cl_2 over 1h. **Procedure C**: **1b** and $(^nBu)_3SnH$ added to vial and dissolved in CH_2Cl_2 (not degassed). To mixture was added the catalyst. **Procedure D**: **1b** and $(^nBu)_3SnH$ added to a vial and dissolved in CH_2Cl_2. In a separate vial was added the catalyst and CH_2Cl_2. The **1b** and $(^nBu)_3SnH$ mixture was added to the catalyst suspension. [d] All yields are those of isolated products. NMR yields in parenthesis: ^1H and ^{19}F NMR yields using ethyl trifluoroacetate as internal reference. [e] 2 mol% catalyst. [f] 10 mol% catalyst.

2.5.3 Scope and Limitations

The optimised reaction conditions were tested against a range of diazo substrates – substitution on the tin hydride was left unchanged as tributylstannanes are the most widely observed organostannane coupling partners involved in Stille-type reactions.[235] Various substituents are tolerated on the diazo unit – alkyl, aryl, halide,

ester, and CF_3 all gave good to moderate yields of the insertion product. However, electron poor *p*ara-nitro-substituted substrates did not afford the desired product **7fa** – instead only protodestannylation product **2.29** (**Scheme 2.17**) was obtained in 68 % isolated yield. Triphenyltin hydride participated in the reaction in a similar fashion to tributyltin hydride, affording good yield of insertion product **7bb**. This procedure proved to be efficient for Ge-H and Si-H insertion, delivering germanane **8ba** and silane **2ba** in good yields.

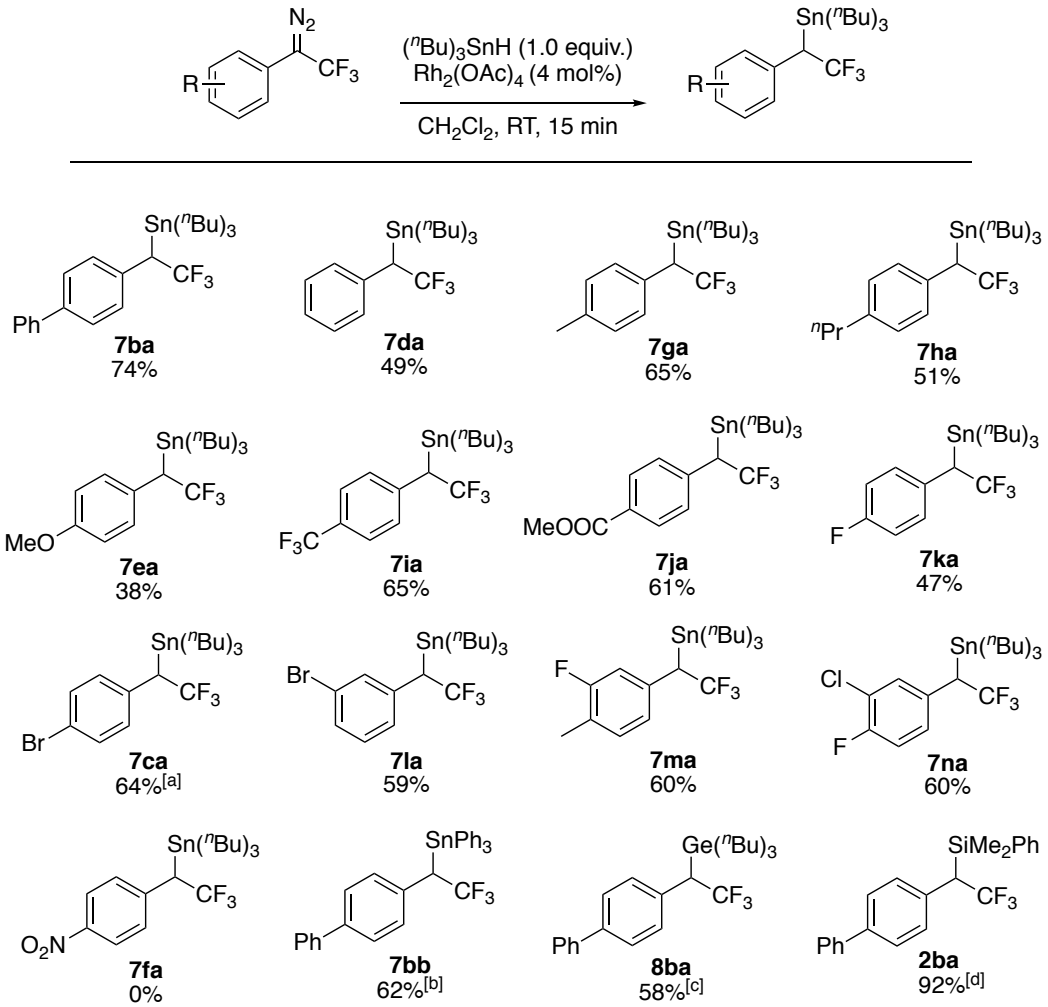
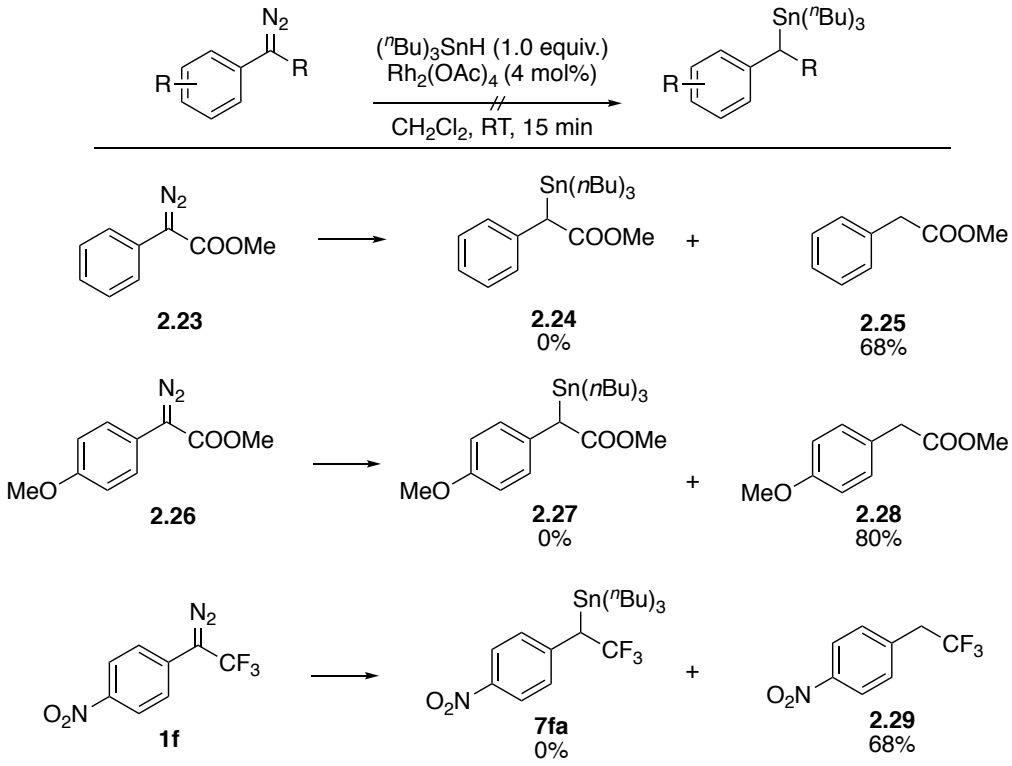


Figure 2.20 Substrate scope: Rhodium-catalysed XHI to Sn-H, Ge-H and Si-H bonds. All reactions performed on 0.1 mmol scale following procedure **D** (**Table 2.5**) unless stated otherwise. All yields are those of isolated products. [a] Procedure **C** (**Table 2.5**). [b] 1.0 eq. of Ph_3SnH used instead, ^1H and ^{19}F NMR yield, using ethyl trifluoroacetate as internal reference. [c] 1.0 eq. of $PhMe_2SiH$ used instead. [d] 1.0 eq. of $(^nBu)_3GeH$ used instead.

When these reaction conditions were applied to diazo esters **2.23** and **2.26** (**Scheme 2.17**), the crude ^{1}H NMR spectra indicated mixtures of stannane and reduction product, however, upon workup only the reduction products, **2.25** and **2.28** respectively, were isolated.



Scheme 2.17 Reactivity of diazoesters against the developed system.

These examples highlight the instability of α-carbonyl stannanes, which is in line with previous reports,[319] and contrasts trifluorodiazoalkanes as a more attractive platform for studying stannane insertion into diazo compounds than their diazo carbonyl counterparts. Given that Wang disclosed α-carbonyl stannanes undergo protodestannylation *via* a putative radical pathway,[319] we hypothesized that an argument based on radical stabilization enthalpy (RSE) – which are derived from bond dissociation enthalpies (BDE) – might explain the differences in stannane stability, and

perhaps account for the, as yet unexplained, single example of a stable α-carbonyl stannane disclosed by Landais (**Figure 2.18**).

There is a lack of experimental tin bond dissociation enthalpies, however α-carbonyl radicals – representative of the intermediate radicals from destannylation – are frequently used as radical initiators in atom transfer radical polymerisation (ATRP) reactions and as such, their structure-activity relationships have been extensively studied.[320] Matyjaszewski and co-workers investigated the effect of radical-stabilising α-substituents on the rate of radical generation from alkyl bromides in the presence of copper (I) bromide (measured as rate of consumption of bromide); substrates bearing both ester and aryl functionality formed radicals 177,000 times faster than substrates bearing only aryl or ester groups alone (**Figure 2.21**).

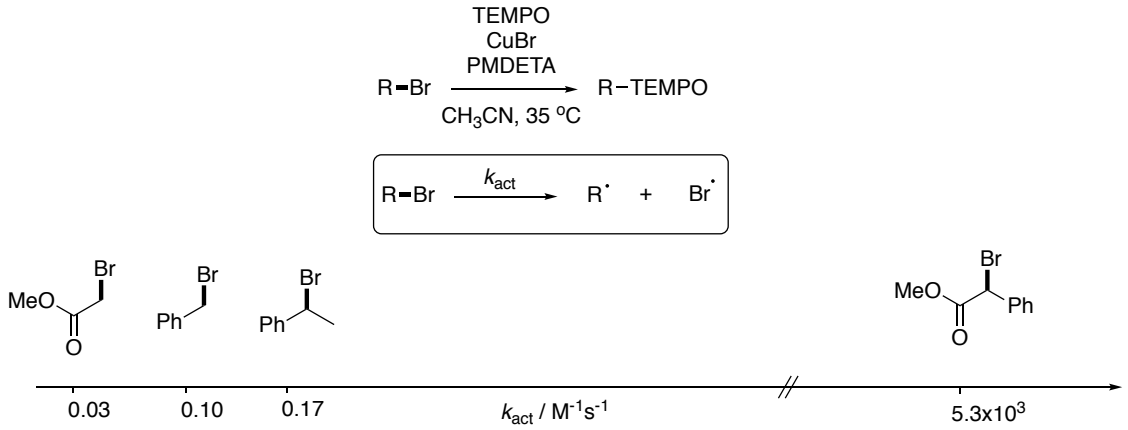


Figure 2.21 Radical-stabilising α-substituents on the rate of radical generation of alkyl bromides.

This study gives credibility to the theory that a radical mechanism is responsible for the observed destannylation, and that radical-stabilising α-substituents promote this pathway (**Figure 2.19**) – at least for stannanes **B** and **C**. Unfortunately, no such rate constant exists for the direct comparison of (1-bromo-2,2,2-trifluoroethyl)benzene to draw a direct comparison for stannane **7da**. However, Ito and coworkers compared

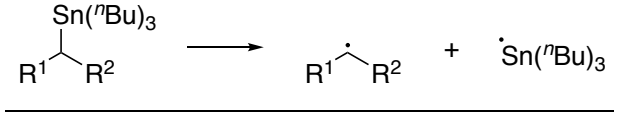
styrene, α-methylstyrene and α-trifluoromethylstyrene in radical polymerisation reactions and found that α-trifluoromethyl groups destabilise carbon-centered radicals,[321] further reinforcing this hypothesis.

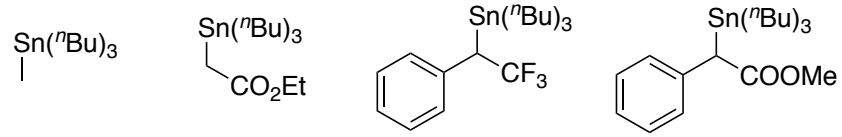
Computational Studies

Computational studies performed by David Ascough.

Due to the paucity of experimental tin bond dissociation enthalpies, quantum mechanical calculations in Gaussian D.0.1 were performed (**Table 2.7**).[322] Computation of tin bond dissociation enthalpies is challenging, due to a lack of experimental data for benchmarking. Both Grindley and Boyd have published recent work on computing organotin dissociation energies; the B3LYP/SDB-aug-cc-pVTZ//B3LYP/def2-SVPD level of theory described therein is applied here.[323,324]

Table 2.7 Computed bond enthalpies in kcalmol^{-1}.[a]





A. **B.** **7da** **C.**

Entry	Stannane	Substituents		BDE/ kcalmol^{-1}	RSE/ Kcalmol^{-1}	Experimental Protodestannylation
		R_1	R_2			
1	**A**	H	H	63.6	0.0	-
2	**B**	H	CO_2Et	58.6	5.0	No
3	**7da**	C_6H_5	CF_3	47.2	16.4	No
4	**C**	C_6H_5	CO_2Me	42.7	20.9	Yes

[a] Values computed at the B3LYP/SDB-aug-cc-pVTZ//B3LYP/def2-SVPD level of theory, as described by Boyd, in Gaussian D.0.1.[323]

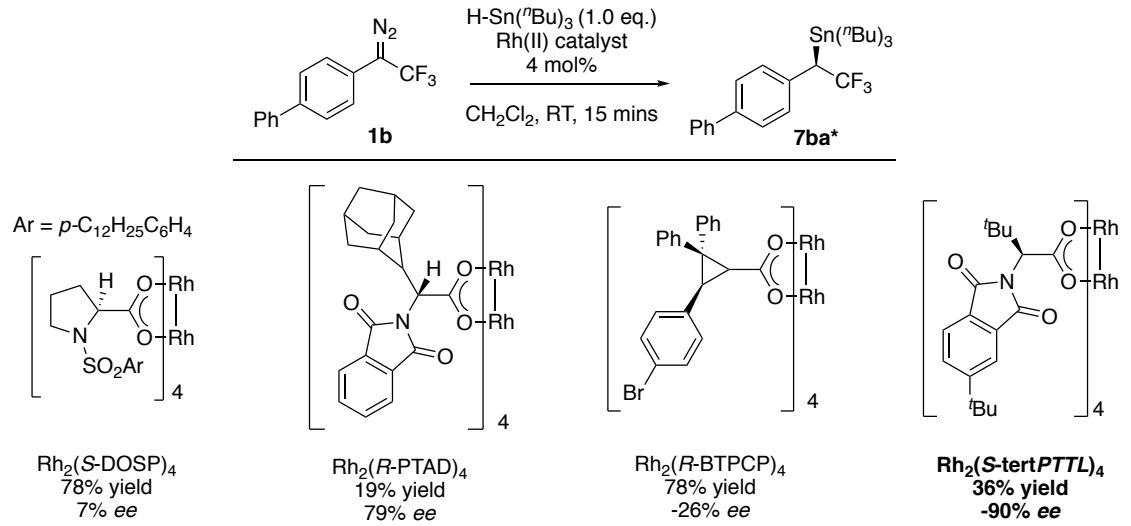
Of the selected organostannanes calculated, the RSE corresponding to Landais' stannane **B** (5.0 kcalmol^{-1}) is significantly lower than the other compounds. This is consistent with a low propensity to protodestannylate *via* radical pathway. In contrast, the phenyl substituted ester **C** has a much higher RSE (20.9 kcalmol^{-1}) consistent with the protodestannylation observed.

Compound **7da** has significantly lower RSE than the corresponding ester substituted derivative **C.** This is again consistent with the observation that α-trifluoromethyl stannanes are resistant to protodestannylation, compared with α-ester stannanes.

2.5.4 Asymmetric Sn-H, Ge-H and Si-H Insertion

The existence of a stereocentre in the XHI products prompted a study into the feasibility of developing an asymmetric variant of the reaction – to date there are no examples of catalytic enantioselective Sn-H insertion reactions.

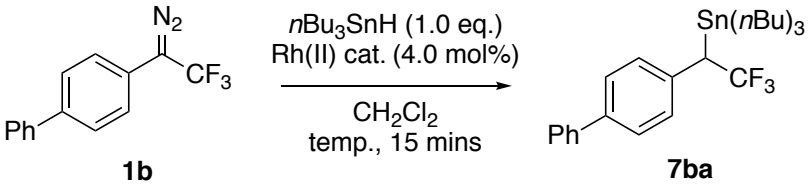
Initially, optimization studies for an asymmetric insertion reaction were performed by testing a range of chiral Rh(II) catalysts (**Scheme 2.18**) which allowed for identification of commercially available Rh_2(*S*-*tert*PTTL)$_4$ as the most efficient catalyst – affording high enantioselectivity of product **7ba** despite being obtained in low yield.



Scheme 2.18 Screening of chiral dirhodium catalysts. Procedure C: **1b** and (^{n}Bu)$_3$SnH added to vial and dissolved in CH_2Cl_2. To mixture was added the catalyst.

When the reaction was performed under inert atmosphere in degassed solvent, a significant improvement of yield was achieved (**Table 2.7, entry 5**). Decreasing temperature improved *ee*, however the yield was diminished (**entries 6 and 7**).

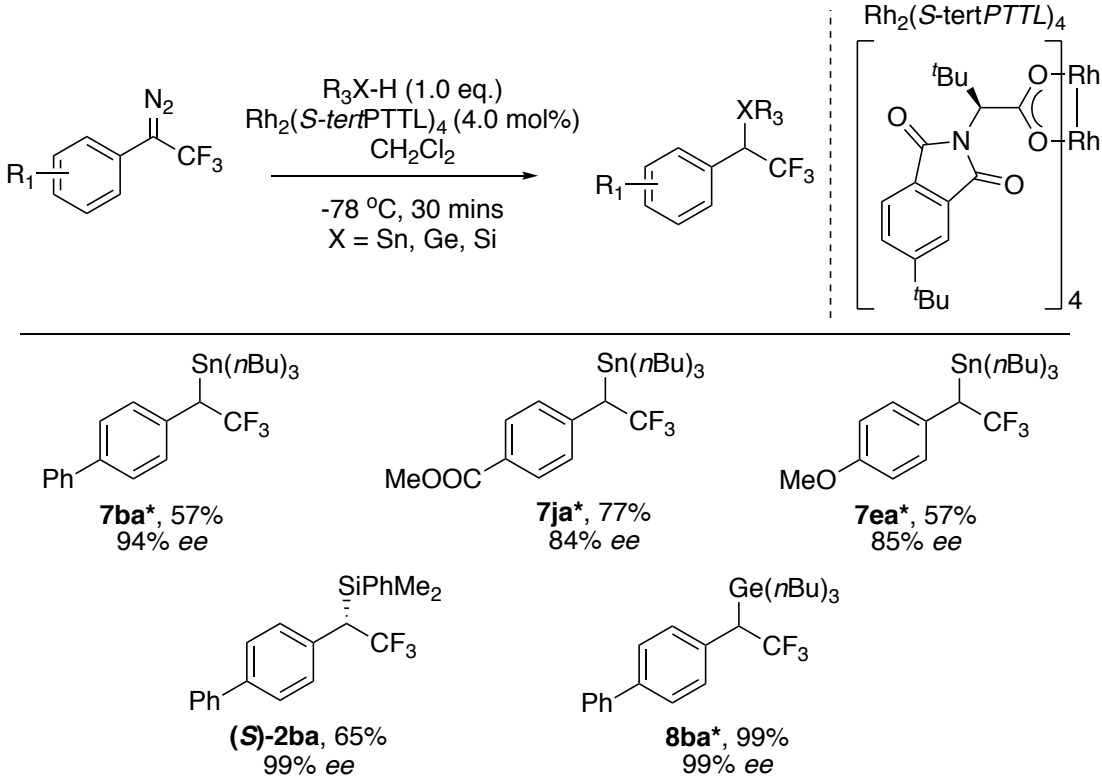
Table 2.7 Optimisation studies for asymmetric Sn-H insertion.



Entry	Catalyst	T/ °C	Yield 2a/ %	*ee*/ %
1[a]	Rh_2(*S*-DOSP)$_4$	RT	78	7
2[a]	Rh_2(*R*-PTAD)$_4$	RT	19	79
3[a]	Rh_2(*R*-BTPCP)$_4$	RT	78	-26
4[a]	Rh_2(*S-tert*PTTL)$_4$	RT	36	-90
5[b]	Rh_2(*S-tert*PTTL)$_4$	RT	82	-91
6[b]	Rh_2(*S-tert*PTTL)$_4$	0	74	-92
7*[b]	**Rh_2(*S-tert*PTTL)$_4$**	**-78**	**57**	**-94**

Yields are those of isolated products. **[a] Procedure A**: **1b** and stannane added to vial and dissolved in CH_2Cl_2. To the mixture was added the catalyst. [b] **Procedure B**: (anhydrous conditions) **1b** and stannane added to a vial and dissolved in CH_2Cl_2. In a separate vial was added the catalyst and more CH_2Cl_2. The **1b**/stannane mixture was added to the catalyst suspension. * Reaction time 30 minutes.

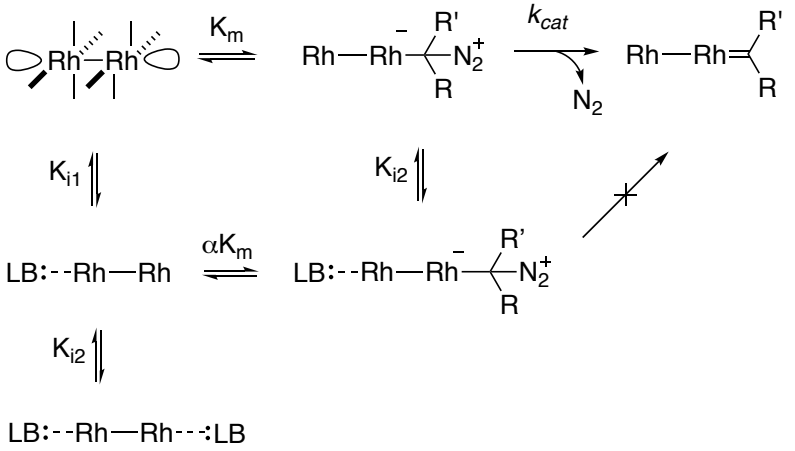
These reaction conditions afforded enantioenriched stannane **7ba** with 57% yield and 94% *ee*. Comparable results were achieved when electron donating 4-methoxy substituted diazo compound **1e** and electron withdrawing ester **1j** were subjected to the asymmetric insertion protocol giving stannanes **7ea** and **7ja** with good to moderate yields with good enantioselectivities. Interestingly, these optimized reaction conditions turned out to be highly efficient for Si-H and Ge-H insertion, which afforded silane **2ba** and germane **8ba** with excellent yield and enantioselectivity (**Scheme 2.19**).



Scheme 2.19 Asymmetric rhodium-catalysed insertion into X-H bonds (X = Sn, Ge, Si).

A detailed kinetic treatment of various rhodium(II) complexes by Pirrung and Morehead has shown that only one of the two available axial coordination sites is catalytically active at any given time (**Scheme 2.17**).[325] They also found that Lewis basic inhibitors may occupy the second coordination site, and that this interaction impedes catalysts – these results are particularly pertinent as substrates for XHI frequently contain Lewis basic

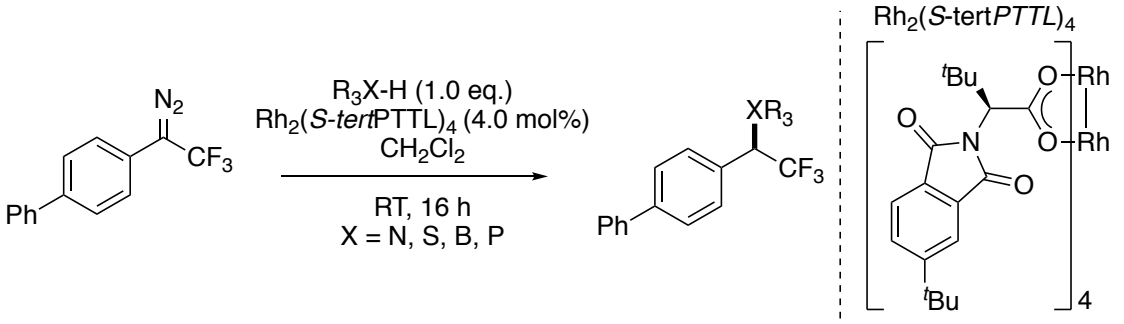
heteroatoms and therefore potentially inhibitory functional group. They also note that in all cases, loss of nitrogen was the rate-determining-step.

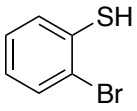


Scheme 2.20 Kinetic analysis of the effect of Lewis basic inhibitors on rhodium(II) catalysts.

When the developed asymmetric rhodium (II)-catalysed conditions were applied to other XHI substrates, no enantioinduction was observed for any other substrate class (**Table 2.8**). This suggests that different mechanisms are operating in the Cu(I) and Rh(II) systems. Furthermore, no insertion was observed in the case of P-H or N-H bearing substrates, despite these substrates smoothly undergoing XHI under copper (I)-catalysis, and in both cases significant quantities of diazo compound remained after 16 h. This indicates catalyst poisoning/inhibition – possibly originating from deactivating interactions highlighted in **Scheme 2.20** – as diazo compounds rapidly undergo dimerization in the presence of transition metals.[285]

Table 2.8 Testing Rh(II)-catalysed XHI against other heteroatoms.



Entry	Substrate	Yield[a]/%	*e.e.*	Comment
1	$Ph_3P.BH_3$	63	rac.	-
2	$(MeO)_2P(=O)H$	0	-	Reaction turned black instantly. 100% recovery of diazo compound.
3		40	rac.	Reaction turned black instantly.
4	$PhNH_2$	trace[b]	-	Reaction turned black instantly. Mostly diazo compound remaining.

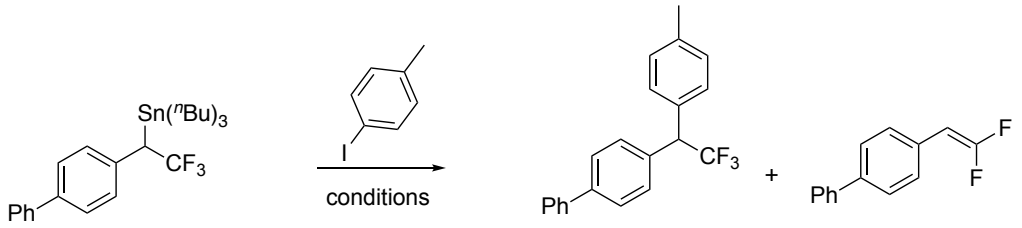
Procedure: Substrate (0.1 mmol) and dirhodium catalyst dissolved in CH_2Cl_2 at room temperature. To the mixture was added diazo compound in a soltion of CH_2Cl_2 and the reaction stirred at room temperature for 16 h. **[a]** Isolated yields. **[b]** Observed by ^{19}F NMR of the crude reaction mixture.

2.5.5 Product Valorization

Investigations into Stille cross-coupling performed by Dr. Janis Veliks.

Stannanes **7** did not participate in Stille cross coupling reactions, as dominant β-fluoride elimination takes place (**Table 2.9**). This is in line with observed reactivity by Molander for similar α-trifluoromethylated alkylboron reagents.[228] This is because palladium – along with many transition metals – have a strong affinity for fluoride, leading to β-fluoride elimination from the intermediate organopalladium in preference to the desired reductive elimination.[99]

Table 2.9 Screening table for Stille coupling.

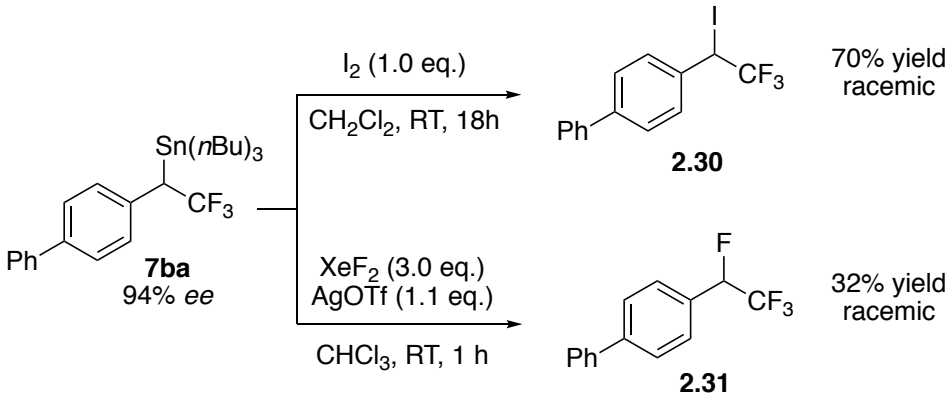


7ba **2.27** **2.28**

Entry	Conditions	Yield[a]		
		7ba	**2.27**	**2.28**
1	$Pd(PPh_3)_4$ (10 mol%), DMF, 60 ˚C, 18 h	-	-	(90)
2	$Pd(PPh_3)_4$ (10 mol%), DMF, RT, 18 h	-	-	(90)
3	DMF, 60 ˚C, 18 h	-	-	(quant.)
4	$Pd(dba)_2$ (3.2 mol%), Ph_3As (12 mol%), LiCl (1.5 eq.), RT, DMF, 18 h	-	-	(quant.)
4	$Pd(PPh_3)_4$ (10 mol%), Toluene, RT, 18 h	(quant.)	-	-
5	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Toluene, 50 ˚C, 18 h	(99)	-	traces
6	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), 1,4-dioxane, 50 ˚C, 18 h	(quant.)	-	traces
7	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), 1,4-dioxane, 90 ˚C, 18 h	(80)	-	(20)
8	Cu(TC) (1.5 eq.), NMP, 0 ˚C to RT	(58)	-	(22)
9	$Pd_2(dba)_3$ (5.0 mol%), CuI (10 mol%), Ph_3As (12 mol%), CsF (1.0 eq.), 80 ˚C, 1,4-dioxane, 18 h	(74)	-	(14)

[a] ^{19}F NMR yield using ethyl trifluoroacetate as internal reference.

The utility of stannanes **7** was demonstrated by performing halogenation reactions (**Scheme 2.21**). (1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylstannane **7ba** smoothly reacts with iodine,[326] affording 4-(2,2,2-trifluoro-1-iodoethyl)-1,1'-biphenyl **2.30** in good yield. Silver mediated fluorination[327] of **7ba** with XeF_2 afforded 4-(1,2,2,2-tetrafluoroethyl)-1,1'-biphenyl **2.31** in moderate yield. However, both cases resulted in loss of stereochemical information.



Scheme 2.21 Halogenation of stannane. Reactions performed by Dr. Janis Veliks.

2.5.6 Summary of Rhodium (II)-Catalysed XHI into Sn-H, Ge-H and Si-H Bonds

The disclosed results offer the first reported asymmetric carbene insertion into Sn-H and Ge-H bonds, for which no other methods exist for generating these enantiopure branched trifluoroethylated organometallic intermediates. The system is also functional for the same transformation with silanes – complementing existing routes to this scaffold. However, when applied to other XHI substrate classes (X = B, P, S, N) no enantioinduction was observed, and in many cases no XHI was observed. This indicates that different pathways dominate for Cu(I) and Rh(II) systems, and that substrate-catalyst compatibility is important. Product valorisation was unfruitful, with stereochemical scrambling observed during halodestannylation and, most disappointingly, β-fluoride elimination under palladium-catalysed cross-coupling conditions.

CHAPTER 3

Radiolabelling the Heteroatom-trifluoroethyl Motif

Chapter 3: Radiolabelling the Heteroatom-trifluoroethyl Motif

3.1 Introduction

3.1.1 Positron Emission Tomography

Positron emission tomography (PET) is a non-invasive functional imaging technique that utilises positron-emitting radioisotopes as labels on tracer compounds. PET is typically used for clinical diagnosis and treatment monitoring; it is also used for drug development. It allows for quantitative measurement of biochemical and physiological processes *in vivo,* including the pharmacokinetics of labelled drugs and their metabolic effects.[328] The ability to provide information on metabolism and molecular events in living patients sets PET apart from purely structural imaging techniques such X-ray or ultrasound.[329]

The most common short-lived radioisotopes for PET are carbon-11, nitrogen-13, oxygen-15, and fluorine-18 (**Table 3.1**). These radionuclides may be used to replace their stable isotopes (^{12}C, ^{14}N, ^{16}O, ^{19}F) without affecting the biological activity of the tracer compound. This differentiates them from other imaging techniques which employ an imaging 'handle' attached to a specific target. These 'handles' are typically large structures which ligate the radionuclide, resulting in significant change in bioactivity of the targeting section and complicating the overall tracer design.[329]

Table 3.1 Production and decay of common PET radionuclides.[330]

Radionuclide	Production	Half-life, $t_{1/2}$/ min	Decay Product	Maximum β^+ energy/ keV	Range (H_2O)/ mm
Carbon-11	$^{14}N(p,\alpha)^{11}C$	20.4	^{11}B	960	4.1
Nitrogen-13	$^{16}O(p,\alpha)^{13}N$	9.97	^{13}C	1190	5.4
Oxygen-15	$^{15}N(d,n)^{15}O$	2.04	^{15}N	1720	8.2
Fluorine-18	$^{18}O(p,n)^{18}F$ $^{20}Ne(d,\alpha)^{18}F$	109.8	^{18}O	635	2.4

The radioisotopes used in PET are produced in cyclotrons – compact particle accelerators capable of producing proton and deuteron beams – by bombardment of a specific target (**Table 3.1**).[330] Due to the relative short half-life ($t_{1/2}$) of these isotopes, preparation of tracers preferably involves installation of the radioisotope in the final step(s) of synthesis – ideally at the same geographical location as isotope production and final imaging. The labelled probe must be synthesised, purified, analysed, and formulated on a minutes and hours time frame. A timescale of three isotope half-lives is loosely applied for the total production time – from end of bombardment (EoB) to injection – so as to ensure there is enough radiolabelled material, at a high enough specific activity, to administer to a subject undergoing the PET scan.[329] Consequently, one of the main challenges in PET is the development of rapid radiosynthetic methods for introducing these short-lived positron-emitting isotopes into the compound of interest.

The positron emitted during the decay process is not detected directly – *in vivo* it only travels a short distance, before annihilating on contact with an electron. Annihilation emits two photons, γ-rays ,approximately 180° apart.[331] A ring of highly sensitive detectors picks up these coincidental γ-rays, initially converting them to light and then electrical impulses *via* a photo-multiplier. These impulses are ultimately processed into a 2D or 3D image of the subject.

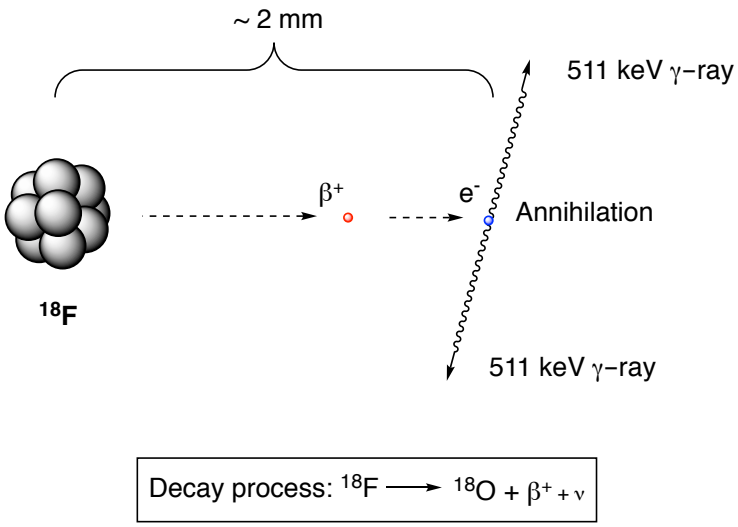


Figure 3.1 Decay process of ^{18}F, resulting in annihilation and production of photons.

The resolution of the final image is dependent on the distance travelled by the positron before annihilation – a shorter range means the annihilation event occurs closer to the decay site and therefore produces a higher resolution image. Fluorine-18 has the lowest mean emission energy of the commonly used radioisotopes (511 keV) and thus has the lowest range (2.44 mm in water).[329]

PET is a very sensitive imaging technique – especially when the tracer is prepared under non-carrier added (n.c.a.) methods – requiring only sub-nanomolar quantities of the tracer.[332] Therefore, the *in vivo* system is not perturbed by the tracer, and so accurate information may be gathered. Furthermore, very potent or toxic compounds may be studied at subpharmacological or subtoxicological doses.

3.1.2 Definition of terms

Molar activity (MA) – For a given radionuclide, molar activity is the activity divided by the mass of all radioactive and stable isotopes of the element involved (units: $Bqmol^{-1}$).[333] A low molar activity radiotracer would mean a higher injection dose is required, potentially causing undesired pharmacological side effects. This can lead to low uptake of ^{18}F-labelled radiotracer due to receptor saturation, resulting in a low-resolution image with high signal-to-noise ratio.[334] Note, 'Becquerel' (Bq) is the agreed SI derived unit for the quantity of activity, and is equal to one disintegration per second.[335]

[^{18}F]Fluorine incorporation (conversion) – ratio of activity incorporated into organic radiochemical compounds versus inorganics radiochemical material.

Radiochemical purity (RCP) – percentage of activity incorporated into a specific tracer. High purity indicates an absence of other radiochemical compounds/species (radiochemically pure samples may contain other non-radioactive chemicals).[335]

Radiochemical conversion (RCC) – The product of [^{18}F]fluorine incorporation and radiochemical purity.

Radiochemical Yield (RCY) – is the amount of activity in the product expressed as the percentage (%) of starting activity, after correction for decay.[335]

Carrier – A chemical species – already present in the preparation, or intentionally added – which will carry a given radionuclide in its associated species through the radiochemical procedure, and/or prevent the radionuclide in its associated species from undergoing non-specific processes due to its low concentration. The carrier is generally isotopic with the radionuclide in question.[333]

No-Carrier-Added (n.c.a.) – A preparation of a given radionuclide where special attention has been paid to procedures, equipment and materials to minimize the introduction of isotopes (both stable and radioactive) of the element in question in the same chemical form or as a species enabling isotopic exchange reactions.[333]

'Hot' mode – pertaining to radiochemical reactions utilising radioactive isotopes.

'Cold' mode – pertaining to reactions conducted with stable isotopes.

Kryptofix (k_{222}) – aminopolyether cryptand which enables the [^{18}F]fluoride ion to be solubilised in a polar aprotic solvent (**Figure 3.2**).[334]

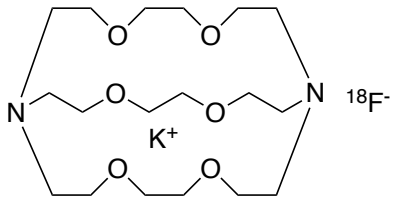


Figure 3.2 [^{18}F]fluoride-k_{222}-K^+ complex.

3.1.3 Current Methods for Radiolabelling the Heteroatom-Trifluoroethyl Motif

Given the pharmaceutical importance of the trifluoroethoxy unit (**chapter 1**), efforts to ^{18}F-radiolabel the motif are valuable; current methods are limited to two disconnections (**Scheme 3.1**): ^{18}F/^{19}F isotope exchange **A**,[336-341] and substitution reactions of anilines/phenols with prefabricated prosthetic groups **B**.[337,342-345] This chapter describes the development of new methodology to realise disconnection **C**.

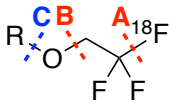
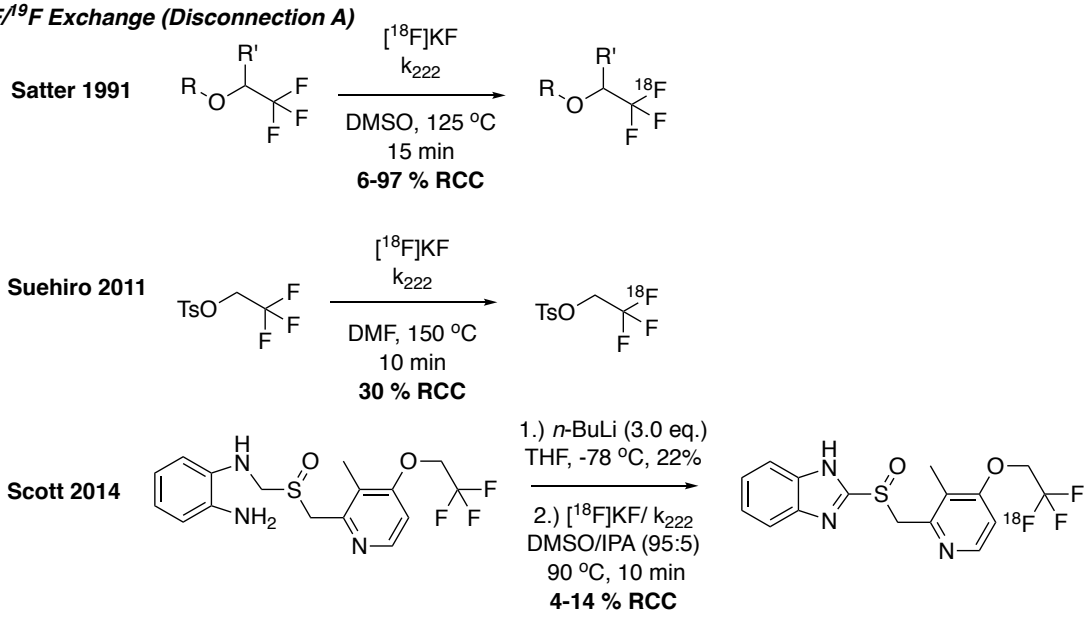


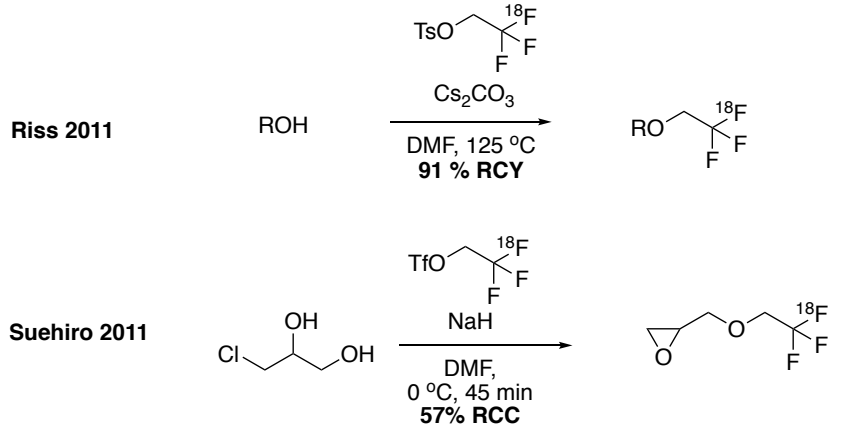
Figure 3.2 A disconnection approach towards ^{18}F-radiolabelling the trifluoroethoxy unit.

^{18}F/^{19}F isotope exchange (disconnection **A**) is generally undesirable as the method inherently produces tracers with low molar activity (**Scheme 3.1)**. The use of prosthetic groups (disconnection **B**) has been applied successfully, however this route necessitates multiple steps after [^{18}F]fluorine incorporation, making it a less attractive technique for the industry. Therefore, an opportunity to supplement these strategies with a complementary method for labelling the trifluoroethoxy unit with ^{18}F-fluoride utilising disconnection **C** was identified. The following section describes three approaches to this end – coupling with [^{18}F]trifluoroethanol, coupling with bromodifluoroethanol followed by ^{18}F/Br halogen exchange, and net H^{18}F addition across a *gem*-difluoroenol ether (**Scheme 3.1)**.

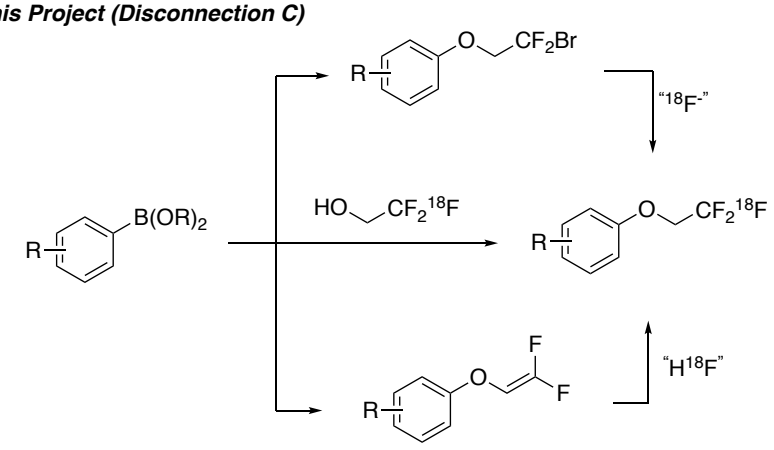
^{18}F/^{19}F Exchange (Disconnection A)



Substitution with ^{18}F-Prosthetic Group (Disconnection B)



This Project (Disconnection C)



Scheme 3.1 Existing methods to access the heteroatom-trifluoroethyl motif in 'hot'-mode, and proposed new route.

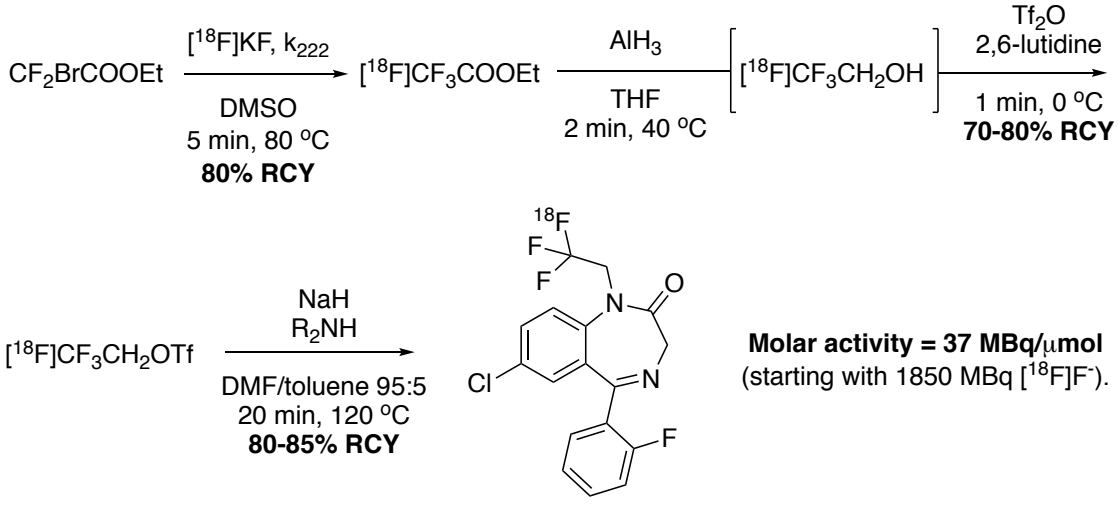
3.2 Chan-Lam Route

3.2.1 Background Information

The following section describes work carried out at AstraZeneca, Macclesfield.

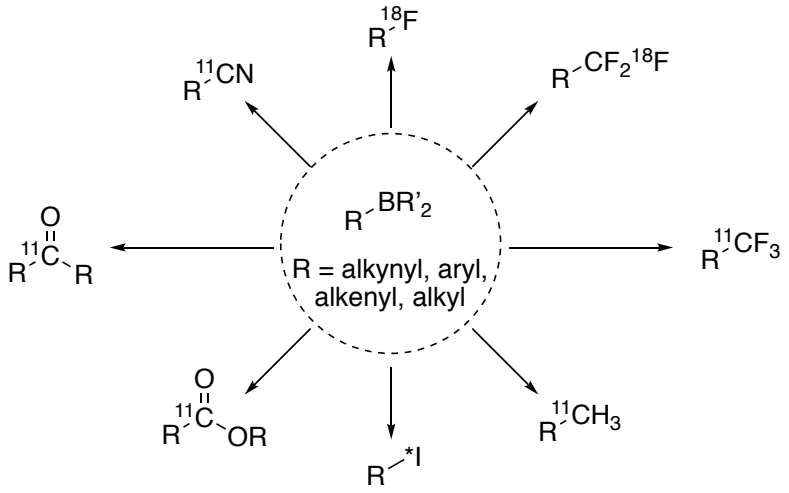
Coupling with [^{18}F]trifluoroethanol

To date, no direct coupling with [^{18}F]trifluoroethanol has been reported, despite the first reported synthesis of [^{18}F]CF_3CH_2OH over 20 years ago.[342] Johnström and co-workers used the [^{18}F]trifluoroethyltriflate prosthetic group – generated *via* [^{18}F]trifluoroethanol – to label secondary amines (**Scheme 3.2**). [^{18}F]CF_3CH_2OH is accessed in two steps from ethyl bromodifluoroacetate: firstly by halogen exchange of bromide for [^{18}F]fluoride, then reduction of [^{18}F]ethyl trifluoroacetate. This section describes attempts to develop the first coupling reaction with [^{18}F]trifluoroethanol.



Scheme 3.2 Radiolabelling of the trifluoroethylamine unit *via* a prosthetic group.

Given the broad utility of boron reagents as precursors in radiochemistry (**Scheme 3.2**),[346] boronic acid/esters were selected as coupling partners for the proposed transformation.

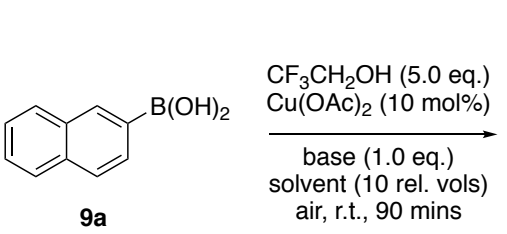


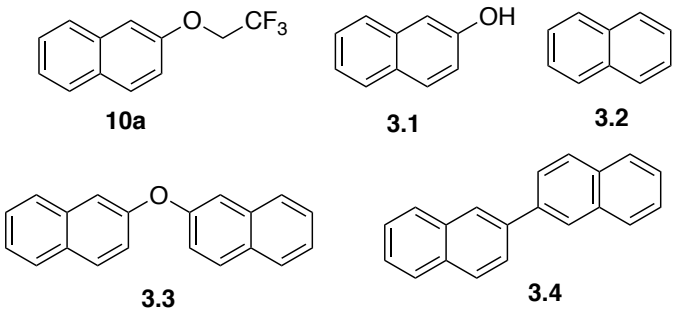
Scheme 3.3 Existing use of boron reagents within the radiochemical community.

3.2.2 Reaction screening

Coupling of trifluoroethanol with boronic species are known in the literature;[37,38,347] however, the only reported coupling of trifluoroethanol with boronic acids uses trifluoroethanol as both coupling partner and solvent.[37] This would not be feasible under ^{18}F-radiolabelling conditions as the resulting tracer would be produced in too low molar activity to be of use, and so development of a more favourable stoichiometry had to be performed. Therefore, extensive screening was conducted to identify reaction conditions that may be translated to ^{18}F-radiolabelling mode (**Table 3.2**).

Table 3.2 Screening of conditions for Chan-Lam coupling of trifluoroethanol with aryl boronic acids.



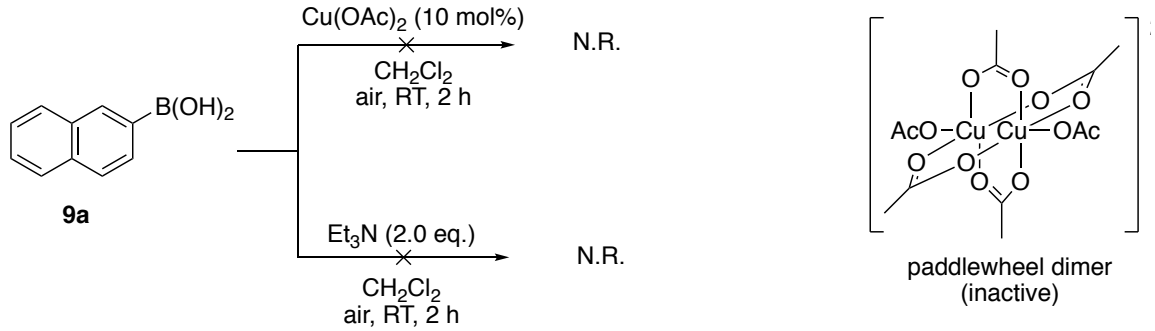


Entry	Solvent	Base	Catalyst	SM 9a/ %	Prod 10a / %	Side Products 3.1/ %	3.2/ %	3.3/ %	3.4/ %
1	DCM	-	$Cu(OAc)_2$	100	**0**	0	0	0	0
2	DCM	Et_3N	-	99	**0**	0	1	0	0
3	DCM	Et_3N	$Cu(OAc)_2$	17	**1**	3	80	0	10
4	DCM	DMAP	$Cu(OAc)_2$	77	**0**	2	7	0	24
5	DCM	1,10-phen	$Cu(OAc)_2$	82	**0**	1	6	1	1
6	DCM	2,6-lutidine	$Cu(OAc)_2$	0	**5**	11	75	1	1
7	DCM	*N*-Me-imidazole	$Cu(OAc)_2$	4	**10**	14	64	2	1
8	DCM	pyridine	$Cu(OAc)_2$	50	**18**	20	8	3	0
9	DCM	pyridine	$Cu(OAc)_2.H_2O$	46	**17**	22	10	2	0
10	DCM	pyridine	$Cu(OTf)_2$	61	**6**	27	17	1	0
11	DCM	pyridine	$Cu(OTf)_2.(pyr)_4$	63	**5**	24	14	3	0
12	DCM	pyridine	$Cu(CF_3CO_2)_2.H_2O$	40	**10**	18	12	5	0
13	DCM	pyridine	$Cu(2\text{-}EH)_2$	49	**12**	20	9	5	0
14	DCE	pyridine	$Cu(OAc)_2$	47	**20**	8	10	5	0
15	$CHCl_3$	pyridine	$Cu(OAc)_2$	49	**20**	13	31	4	0
16	CH_3CN	pyridine	$Cu(OAc)_2$	80	**6**	6	0	0	0
17	THF	pyridine	$Cu(OAc)_2$	26	**17**	16	21	6	16
18	2-Me-THF	pyridine	$Cu(OAc)_2$	31	**15**	15	26	5	4
19	MTBE	pyridine	$Cu(OAc)_2$	62	**14**	9	5	3	1
20	Et_2O	pyridine	$Cu(OAc)_2$	77	**9**	5	4	1	0
21	acetone	pyridine	$Cu(OAc)_2$	53	**14**	11	8	4	3
22	**IPAc**	**pyridine**	$Cu(OAc)_2$	**37**	**23**	**9**	**21**	**5**	**1**
23	EtOAc	pyridine	$Cu(OAc)_2$	14	**13**	10	22	3	1
24	BuOAc	pyridine	$Cu(OAc)_2$	44	**22**	31	44	6	1

Procedure: **A**, copper source, internal standard (4,4'-di-*tert*-butylbiphenyl, 22.6 mg) and solvent (1.8 mL) were charged to a stem block. 2,2,2-trifluoroethanol was added, followed by base. The reaction was stirred at room temperature for 30 minutes, then 30 °C for 30 minutes, then 40 °C for 30 minutes. 1,10-phen = 1,10-phenanthroline. $Cu(2\text{-}EH)_2$ = copper(II) (2-ethyl hexanoate)$_2$. All yields are HPLC assay yields. **SM** = starting material. **Prod** = desired product.

When the boronic acid is exposed to only triethylamine or copper catalyst it is stable to degradation (**entries 1 & 2**), indicating the system requires both amine base and copper catalyst to be active. This is consistent with a report by the Stahl group, who

demonstrated that in the absence of Lewis bases, the $Cu(OAc)_2$ forms a paddlewheel structure (**Scheme 3.4**). This dimeric (or tetrameric) copper complex species is unreactive towards oxidative coupling and must denucleate to facilitate oxidative coupling. Addition of Lewis bases facilitates this denucleation and hence promotes oxidative coupling.[348,349]

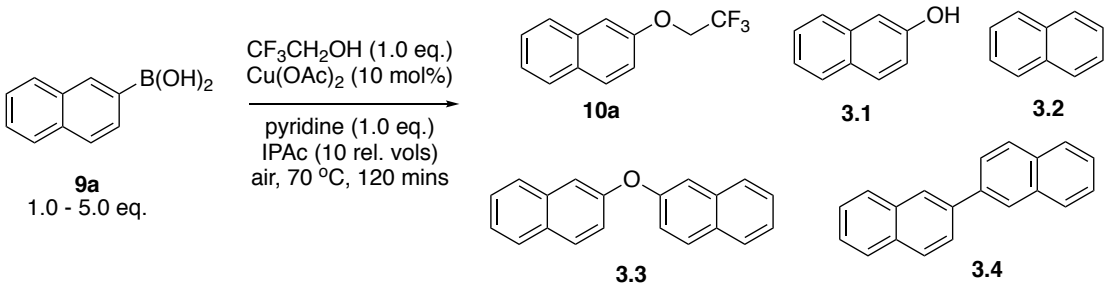


Scheme 3.4 No reactivity without both copper catalyst and organic base.

Screening of bases (**entries 3-8**) identified pyridine as the best. Whilst variation of the copper catalyst (**entries 8-13**) showed that the classical Chan-Lam catalyst copper (II) acetate gave the best result. Finally, screening solvents identified isopropyl acetate (IPAc) as the best solvent (**entries 14-24**). Ultimately, the best conditions consisted of heating boronic acid at 40 ^{o}C with trifluoroethanol (5.0 eq.) in the presence of pyridine and $Cu(OAc)_2$ catalyst in isopropyl acetate solvent, generating the desired product in 23 % yield (**entry 22**). Protodeboronation – to yield naphthalene **3.2** – proved to be the dominant pathway in most cases.

Since alternative pathways dominate when boronic acid is limiting, trifluoroethanol was examined as limiting reagent, with sacrificial excess of boronic acid (**Table 3.3**). Unfortunately increasing the loading of boronic acid impedes the reaction – with protodeboronation the primary pathway.

Table 3.3 Investigation of Stoichiometry..

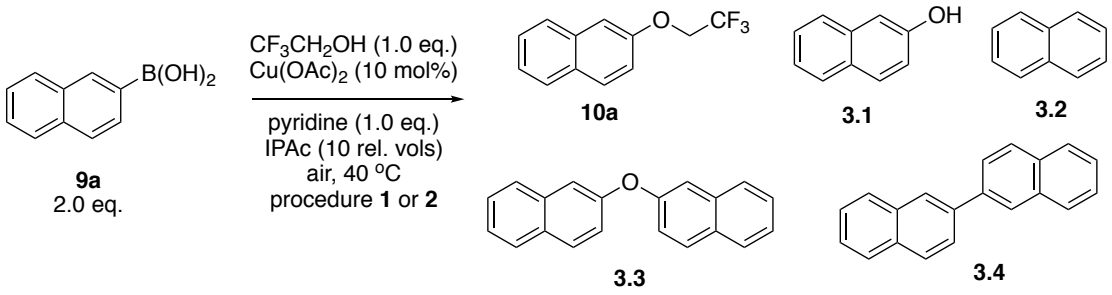


Entry	Eq. 9a	Yield 10a/ %	Major Species
1	1.0	9	3.2
2	2.0	8	3.2
3	3.0	3	3.2
4	4.0	2	3.2
5	5.0	1	3.2

Procedure: A, $Cu(OAc)_2$, internal standard (4,4'-di-*tert*-butylbiphenyl, 22.6 mg) and solvent (1.8 mL) were charged to a stem block. 2,2,2-trifluoroethanol was added, followed by base. The reaction was stirred 70 ^{0}C for 120 mins. HPLC yield of other products not possible as detector is saturated with large excess of starting material.

Since excess boronic acid self-promotes protodeboronation, a series of syringe pump experiments were undertaken to slowly add the boronic acid to the reaction mixture (**Table 3.4**). Addition over 2 hours gave a yield of 18 % of **10a**, an improvement on the 8 % observed with the all-in batch procedure (**entries 1 & 2**). Addition over 7 hours (**entry 4**) yielded the desired product in a slightly improved 29 % yield, however this procedure is fundamentally opposed to the rapid synthesis required for PET. Note, increased catalyst loading resulted in reduction of yield in favour of formation of side products (**entries 2 & 3**).

Table 3.4 Investigation of Rate of Addition.

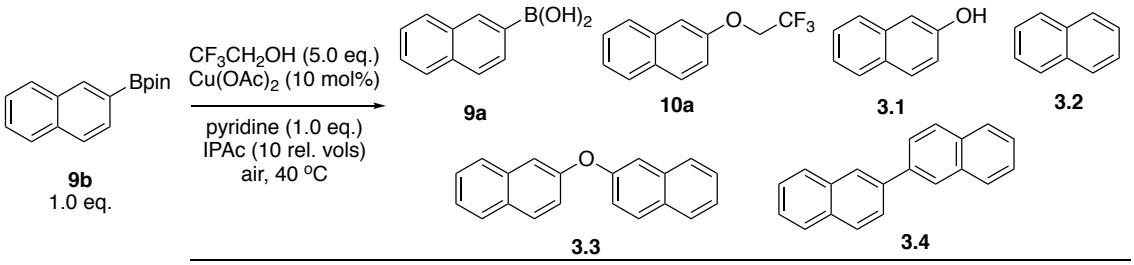


Entry	Cat. Loading/ mol%	Procedure	Yield 10a/ %	Major species
1	10	1	8	3.2
2	10	2[a]	18	3.2
3	50	2[a]	12	3.2
4	10	2[b]	29	10a

Procedure 1: 2-naphthylbornic acid (A), $Cu(OAc)_2$, internal standard (4,4'-di-*tert*-butylbiphenyl, 22.6 mg), 4 AMS, and solvent (1.8 mL) were charged to a stem block. 2,2,2-trifluoroethanol was added, followed by base and the reaction stirred for 120 minutes at 40 °C. **Procedure 2**: $Cu(OAc)_2$, internal standard (4,4'-di-*tert*-butylbiphenyl, 22.6 mg), 4 AMS, and solvent (1.0 mL) were charged to a stem block. The reaction mixture was heated to 40 °C and 2,2,2-trifluoroethanol added, followed by base. At this point, addition of a solution of 2-naphthylbornic acid (A), in IPAc (2 mL) was initiated. **[a]** addition over 2 hours. **[b]** 1.05 equivalents of 2-naphthylboronic acid used, addition of which was over 7 hours.

Given the propensity for the boronic acid to undergo protodeboronation with relative ease, the best (non-syringe pump) conditions were tested against boronic pinacol ester for the oxidative coupling with trifluoroethanol (**Table 3.5**).

Table 3.5 Investigation of coupling with Boronic Pinacol Esters.



	SM	Product	Side Products				
Entry	**9b/%**	**9a/ %**	**10a / %**	**3.1/ %**	**3.2/ %**	**3.3/ %**	**3.4/ %**
1	54	46	**1**	1	0	0	0
2[a]	33	9	**36**	14	0	8	0
3[b]	17	7	**37**	8	10	13	0
4[b,c]	80	14	**5**	1	0	1	0
5[b,d]	67	18	**2**	16	14	2	0
6[b,e]	27	6	**42**	13	4	8	0

[a] = 70 °C, 90 mins. [b] = 70 °C, 16h. [c] Reaction performed with 1.0 eq. pinacol. [d] Reaction performed with 1.0 eq. $B(OH)_3$. [e] Reaction performed under oxygen environment. **SM** = starting material.

When the best conditions for boronic acids were used (**entry 1**), only trace product was observed, with boronic ester hydrolysis to the boronic acid being the only significant transformation. However, on heating the reaction to 70 °C, the desired product was formed in 36 % yield – an improvement on boronic acids (**entry 2**). However, the reaction stalled, with no further product formation when left overnight at this temperature (**entry 3**). This may be attributed to the effect of pinacol in Chan-Lam oxidative couplings, which can cause catalyst inhibition; pinacol – liberated either by hydrolysis of the organoboron starting material or of the organoboron byproduct following the transmetalation event – is thought to form a catalytically inactive $Cu(II)pin_2$ complex with the catalyst (**figure 3.2**).[350] Indeed, spiking the reaction with an equivalent of pinacol was detrimental to the reaction (**entry 4**).

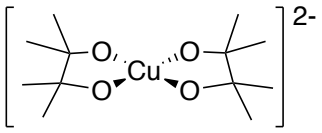


Figure 3.3 Cu(II)(pinacol)$_2$ complex.

Watson and co-workers overcame this problem for Chan-Lam aminations by using boric acid, B(OH)$_3$ which forms stable boric acid esters with diols, to remove free pinacol from the reaction (**Figure 3.4**).[351]

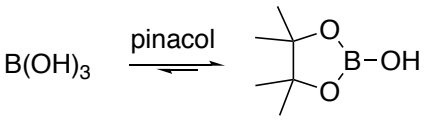
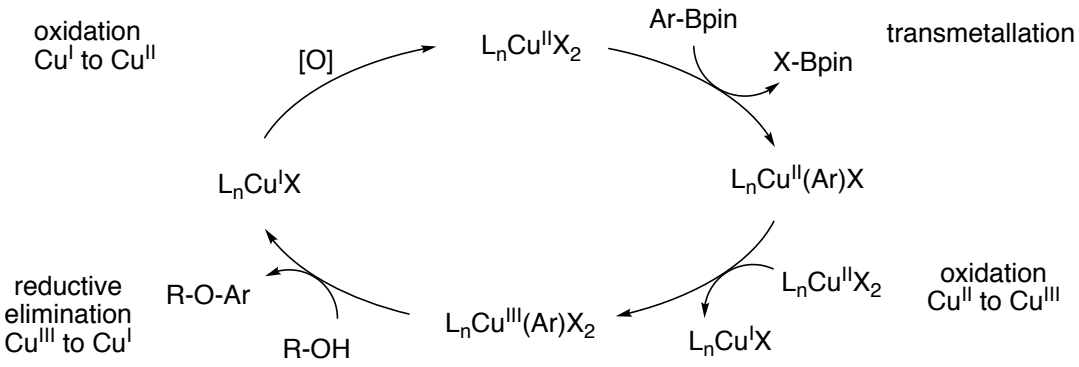


Figure 3.4 HOBpin formation.

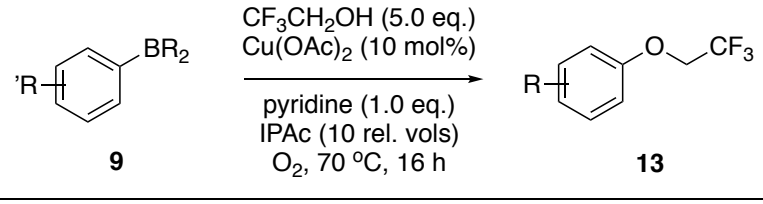
Furthermore, they suggested that the formation of side products – in particular, the protodeboronation product – was accelerated by the presence of Cu(I) species in the catalytic cycle (**Scheme 3.4**). They found that boric acid additionally accelerates re-oxidation from Cu(I) to Cu(II), thereby reducing the competing pathway. Unfortunately, this did not work in the case of etherification with trifluoroethanol (**entry 5**).

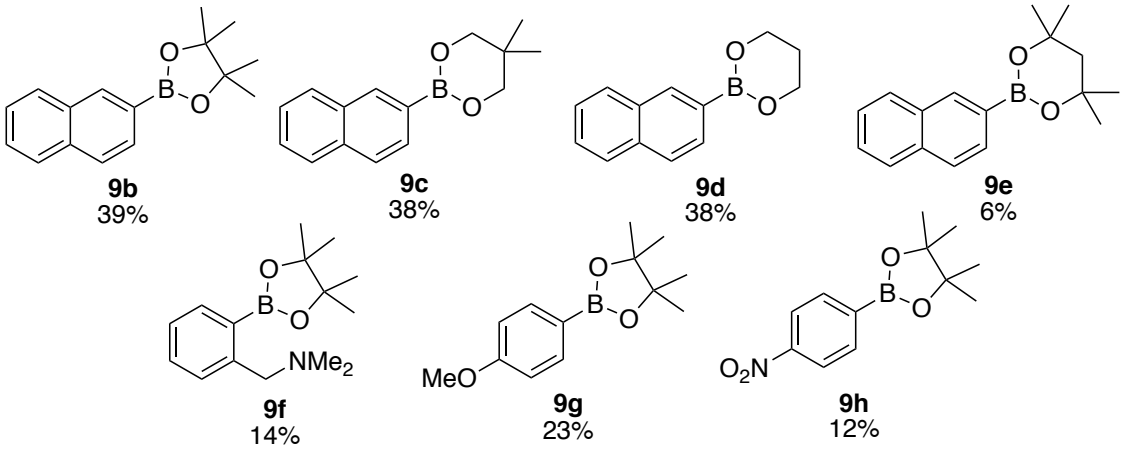


Scheme 3.4 Chan-Lam catalytic cycle.

A screen of boronate esters was conducted (**Table 3.6**); variation of the diol from pinacol **9b**, to neopentyl glycol **9c** or 1,3-propanediol **9d** offered no improvement. 2,4-dimethylpentane-2,4-diol **9e** offered a greatly diminished 6% yield. Boronate ester **9f** gave a disappointingly poor 14% yield; Clark and co-workers demonstrated that boronate esters bearing a pendant amine react more efficiently than those without, as the amine group can coordinate to the catalyst and facilitate coupling.[352] Electronically rich **9g** or poor **9h** boronate esters both performed worse than neutral boronates **9b-d**.

Table 3.6 Screening of Different Boronate Species. All yields determined by ^{19}F NMR using α,α,α-trifluorotoluene.



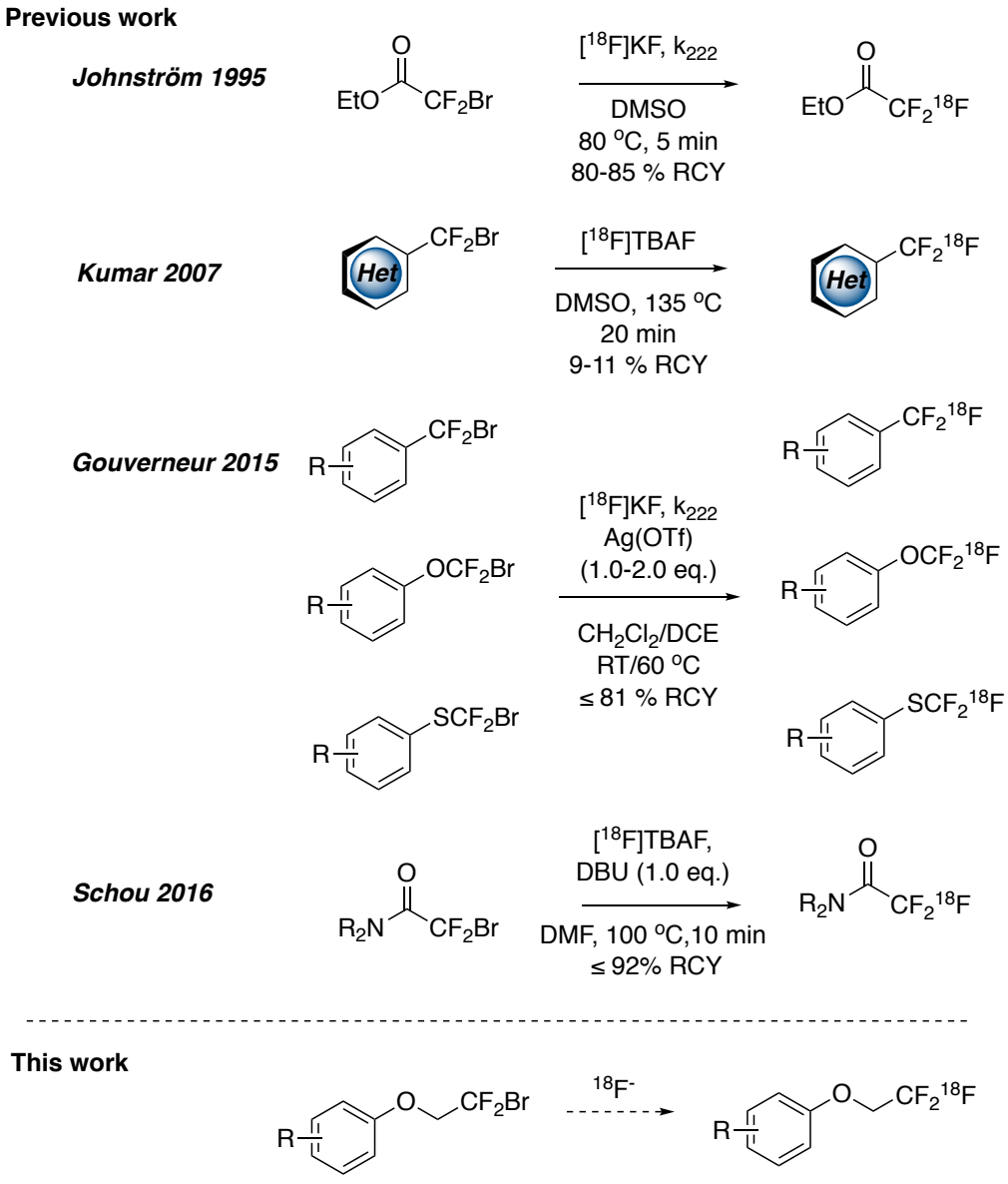


Despite exhaustive attempts, the coupling of trifluoroethanol with aryl boronic acids/esters proved untranslatable to PET, as the cold reaction indicated that large excess of the boronate starting material – representative of radiochemical conditions – favoured the formation of side products over the desired product. Accordingly, it was decided to investigate labelling of the trifluoroethoxy unit *via* an alternative route.

3.3 Halogen Exchange Route

3.3.1 Previous work

Given that halogen exchange has successfully been employed in the labelling of the trifluoromethyl group in various scaffolds – such as trifluoroacetamides,[353] ethyl trifluoroacetate,[342] aryl-CF_3, aryl-OCF_3 and aryl-SCF_3[354-356] – the next approach investigates a similar strategy for the labelling of the trifluoroethyl motif, Aryl-OCH_2CF_3 (**Scheme 3.5**).

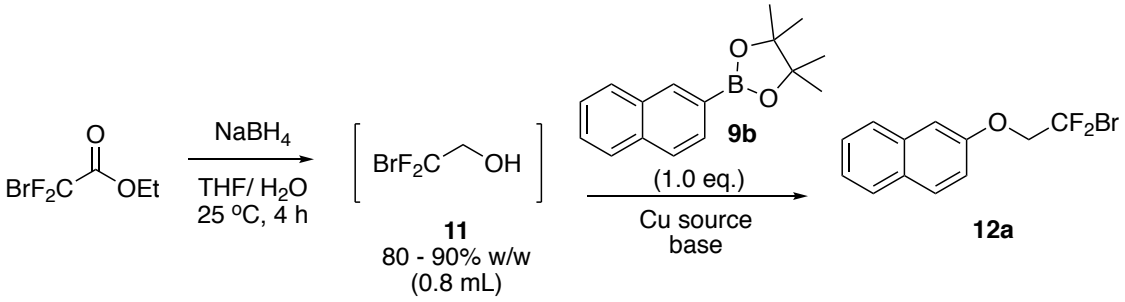


Scheme 3.5 Proposed labelling of the trifluoroethoxy unit *via* halogen exchange.

3.3.2 Precursor Synthesis – Reaction Development

The precursor for the proposed halex reaction, aryl-OCH_2CF_2Br, is not reported in literature., A Chan-Lam coupling of bromodifluoroethanol **11** with aryl boronic acids was therefore proposed. Bromodifluoroethanol **11** – made by borohydride reduction of ethyl bromodifluoroacetate – was tested against model coupling partner, 2-naphthyl pinacol boronic ester (**Table 3.6**).[357,358]

Table 3.6 Reaction optimisation – coupling of bromodifluoroethanol with boronic pinacol ester.



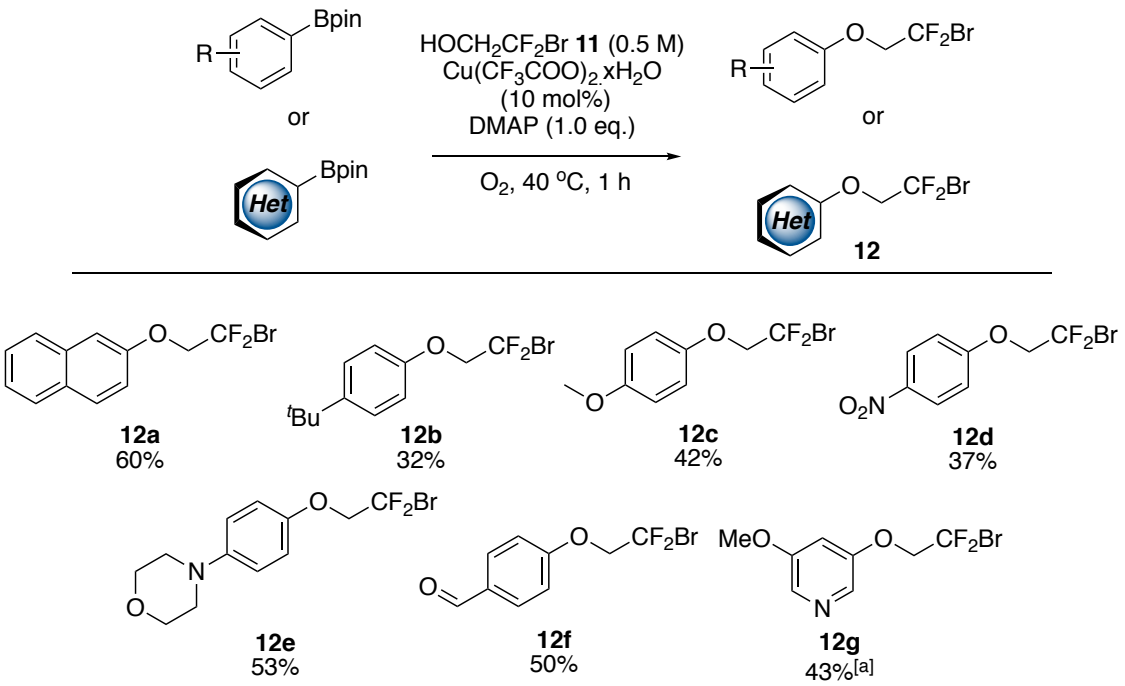
Entry	Cu source	Cu loading/ mol%	base	Base loading/ eq.	Yield/ %[a]
1	$Cu(OAc)_2$	10	DMAP	1.0	49
2	$Cu(OAc)_2$	10	Pyridine	1.0	0
3	$Cu(OAc)_2$	10	Et_3N	1.0	0
4	$Cu(OAc)_2.H_2O$	10	DMAP	1.0	48
5	$Cu(2\text{-}EH)_2$	10	DMAP	1.0	18
6	**$Cu(CF_3COO)_2.xH_2O$**	**10**	**DMAP**	**1.0**	**63 (60)**
7	$Cu(CF_3COO)_2.xH_2O$	5	DMAP	1.0	61
8	$Cu(CF_3COO)_2.xH_2O$	25	DMAP	1.0	54
9	$Cu(CF_3COO)_2.xH_2O$	50	DMAP	1.0	47
10	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	0.5	45
11	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.5	58
12	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.0	40[b]
13	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.0	33[c]
14	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.0	57[d]
15	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.0	7[e]
16	$Cu(CF_3COO)_2.xH_2O$	10	DMAP	1.0	8[f]
17	$Cu(CF_3COO)_2.xH_2O$	10	-	-	0
18	-	-	DMAP	1.0	0
19	-	-	-	-	0

Procedure: 2-naphthyl pinacol boronic ester, copper catalyst and base (if solid) added to a vial and purged with O_2. Bromodifluoroethanol added and base (of liquid) added. Solution stirred at 40 °C for 1 h. **[a]** ^{19}F-NMR yields using trifluorotoluene as internal standard. Isolated yields shown in parenthesis. Cu(2-EH) is Copper (II) (2-ethyl hexanoate). **[b]** Reaction performed at 25 °C for 4 h. **[c]** Reaction performed at 70 °C. **[d]** Reaction conducted with 4 angstrom molecular sieves. **[e]** Reaction conducted under nitrogen atmosphere. **[f]** Reaction conducted under air.

When reported conditions for coupling with trifluoroethanol as solvent were employed, the desired product **12a** was observed in 49 % yield (**entry 1**). Exploration of bases identified DMAP as the optimal (**entries 1-3**), with further screening identifying copper(II) trifluoroacetate hydrate as the best catalyst (**entries 3-6**). Variation of copper- and base-loading gave no further improvement (**entries 7-11**). Probing reaction temperature identified 40 ^{o}C as optimal (**entry 6 vs entries 12 & 13**) and in the absence of an oxidising atmosphere the reaction stalls (**entry 6 vs entries 15 & 16**). The reaction did not proceed without both catalyst and base (**entries 17-19**).

3.3.3 Substrate Scope

The optimal conditions were tested against a range of substrates, with the reaction affording the novel bromodifluoroethoxy motifs on substrates bearing a variety of functionalities and electronic properties (**scheme 3.6**). The reaction worked on electronically neutral substrates **12a** and **12b**, as well as electronically rich and poor substrates – affording *para*-methoxy product **12c** and *para*-nitro product **12d** in 42 % and 37 % isolated yields respectively (Hammett constants: OMe σ_{para} = -0.27; NO_2 σ_{para} = 0.78).[310] The reaction also tolerates functional groups, such as morpholine and aldehyde – yielding products **12e** and **12f** in 53 % and 50 % isolated yields respectively. Coupling of bromodifluoroethanol could be achieved on heteroaromatic systems too, although the reaction required higher temperatures and longer reaction times to yield pyridine-based product **12g** in 43 % yield. In all cases protodeboronation was a major side product.



Scheme 3.6 Substrate scope of bromodifluoroethanol coupling. [a] 80 °C for 3 h.

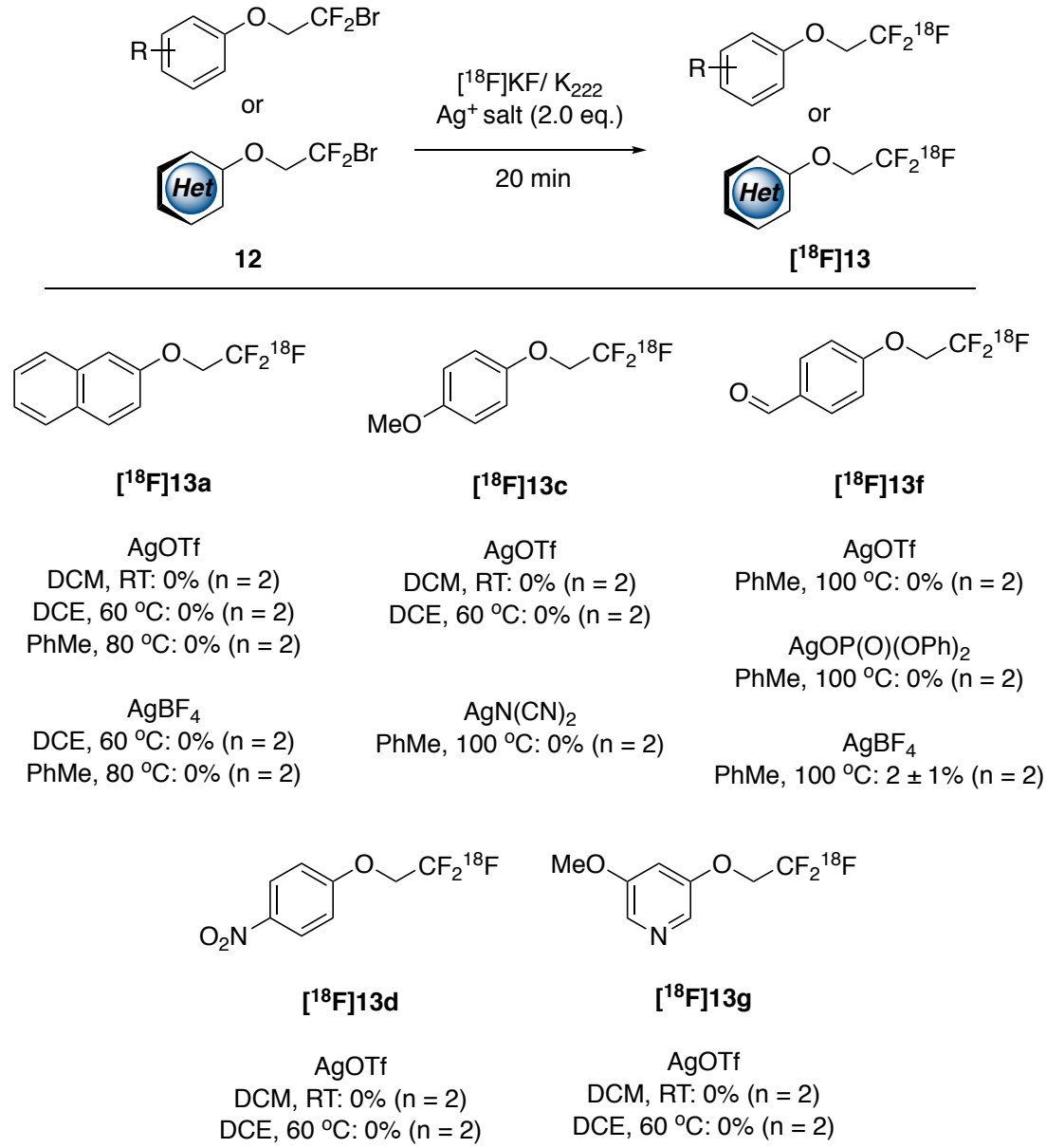
3.3.4 ^{18}F halogen exchange

Labelling experiments in section **3.3.4** conducted at the Siemens Oxford Molecular Imaging Laboratory (SOMIL) by Dr. Stefan Verhoog, Thomas Wilson and Jeroen Sap.

Halogen exchange (halex) applied to ^{18}F-labelling of trifluoromethyl groups, from R-CF_2X precursors, relies on thermal activation only – generally requiring high temperatures and/or relatively long reaction times.[354,359-362] This method has met with limited success, since the presence of two α-fluorine atoms severely inhibits substitution at this centre with fluoride.[363,364] Dolbier and co-workers observed the rate of S_N2 at the CF_2Br site to be at least 13,000 times slower than for the corresponding CH_2Br substrate.[365]

Gouverneur and co-workers recently exploited the affinity of silver salts for halides to achieve R-CF_2Br bond displacement with [^{18}F]fluoride under mild conditions – an

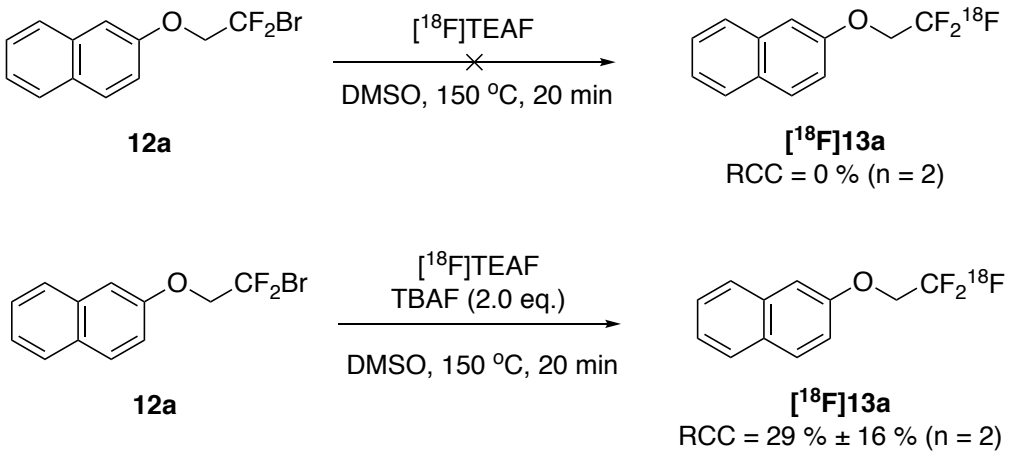
unfeasible transformation without the presence of a silver salt.[355] When these conditions were applied to the novel bromodifluoroethyl substrates, no halex was observed even at significantly elevated temperatures (**Scheme 3.7**).



Scheme 3.7 ^{18}F halogen exchange.

Given that Br/^{18}F halogen exchange was not successful with [^{18}F]KF, other $^{18}F^-$ sources were tested; [^{18}F]tetraethylammonium fluoride gave no conversion under non carrier added (n.c.a.) conditions. However, when the reaction was carried out in the presence of

2.0 equivalents of tetrabutylammonium fluoride as a carrier, the desired product was observed in 29% RCC (± 16 %, n = 2) (**scheme 3.8**).



Scheme 3.8 Radiolabelling the trifluoroethoxy motif with [^{18}F]TEAF.

3.3.5 Mechanistic Studies

This prompted a mechanistic study into the proposed Br/F halogen exchange (**Figure 3.5**). Within 10 mins, almost complete conversion to the trifluoromethyl product is observed; however, two sets of doublets of doublets are observed, which disappear as the reaction proceeds – these correspond to *gem*-difluoroenol ether **14a** (**Figure 3.5**). It was hypothesised that this is the reaction intermediate, and that ^{18}F incorporation is in fact by net H^{18}F addition across the double bond – with the first equivalent acting as a base to eliminate HBr from the substrate.

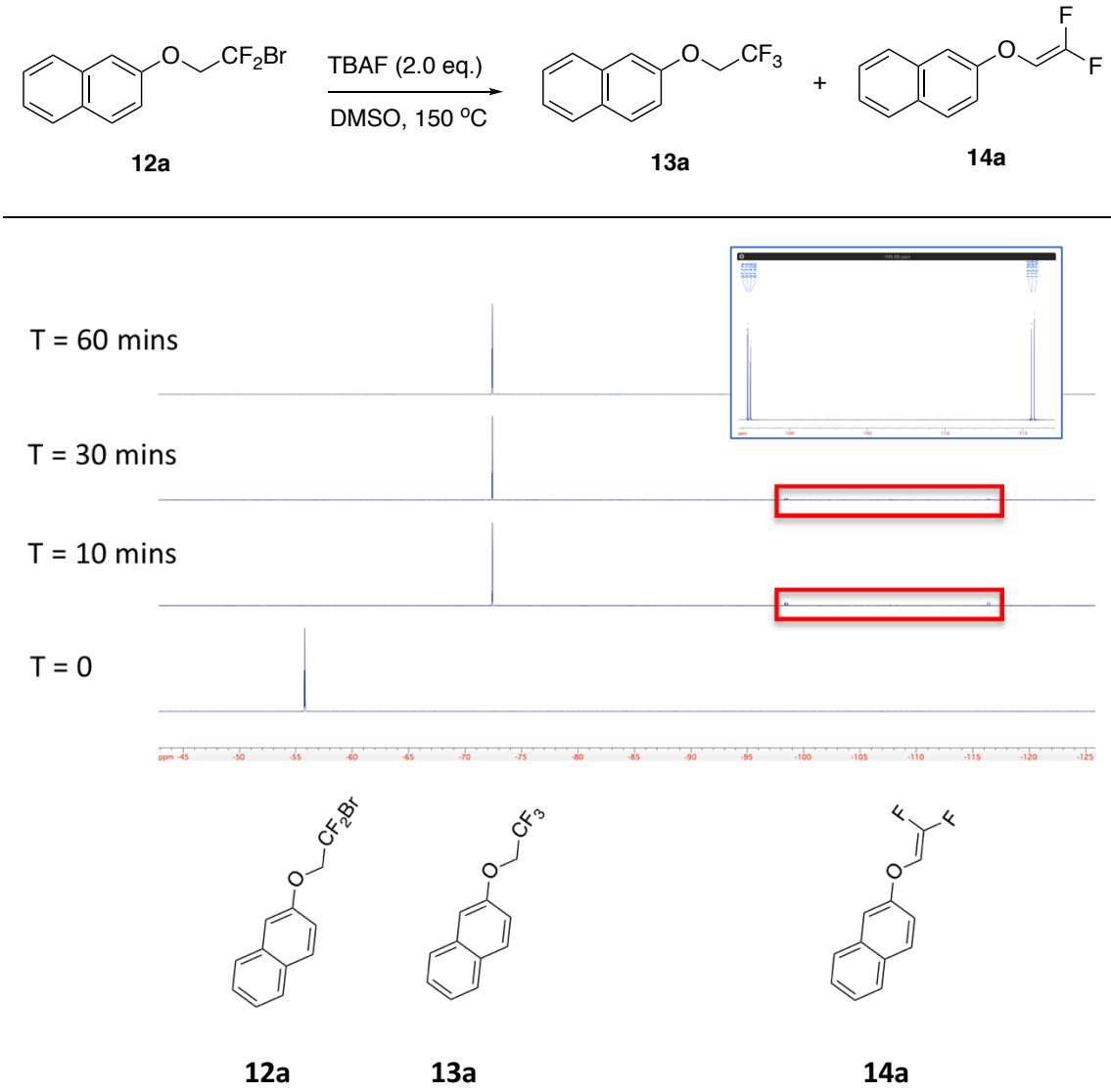
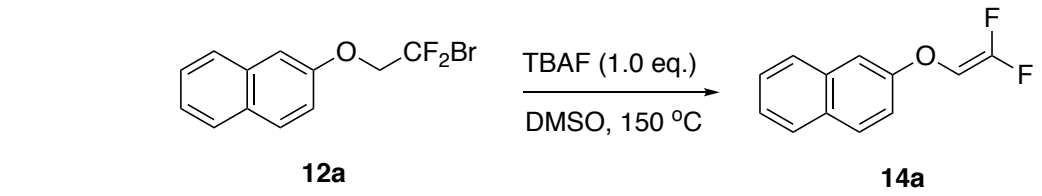


Figure 3.5 Profiling reaction of **12a** with 2.0 eq. TBAF.

A control reaction was performed using only one equivalent of TBAF – this time complete conversion to the *gem*-difluoroenol ether **14a** was observed (**Figure 3.6**).



12a **14a**

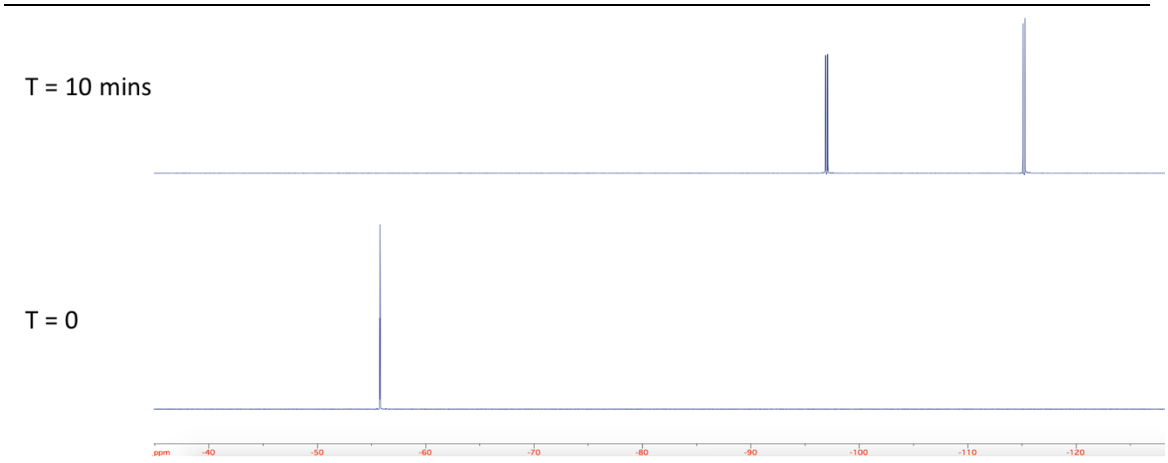
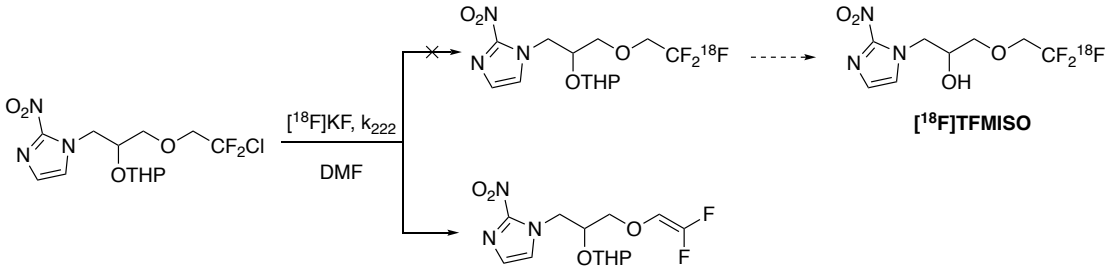


Figure 3.6 Profiling reaction of **12a** with 1.0 eq. TBAF.

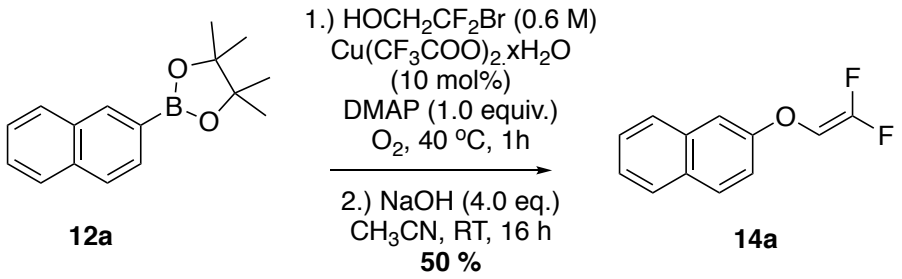
Suehiro and co-workers observed a similar result in their attempted n.c.a. Cl/^{18}F exchange to label the tumour hypoxia marker trifluoromisonidazole (TFMISO) (**Scheme 3.9**).[337]



Scheme 3.9 Attempted ^{18}F/Cl halex by Suehiro and co-workers.

This is perhaps unsurprising, since α,α-difluoro units are known to enhance elimination of R-CF_2X substrates;[366] Dolbier Jr. and co-workers demonstrated experimentally that the rate of HBr elimination from *n*-alkyl-CF_2Br substrates is 59 times faster than from *n*-alkyl-CH_2Br.[365]

Given that *gem*-difluoroenol ether **14a** was identified as the true precursor, a one-pot synthesis to form **14a,** was developed (**scheme 3.10**). Evaporation of excess bromodifluoroethanol, followed by re-dissolution in acetonitrile and addition of sodium hydroxide afforded the *gem*-difluoroenol ether **14a** in 50 % yield.



Scheme 3.10 One-pot synthesis of *gem*-difluoroenol ether.

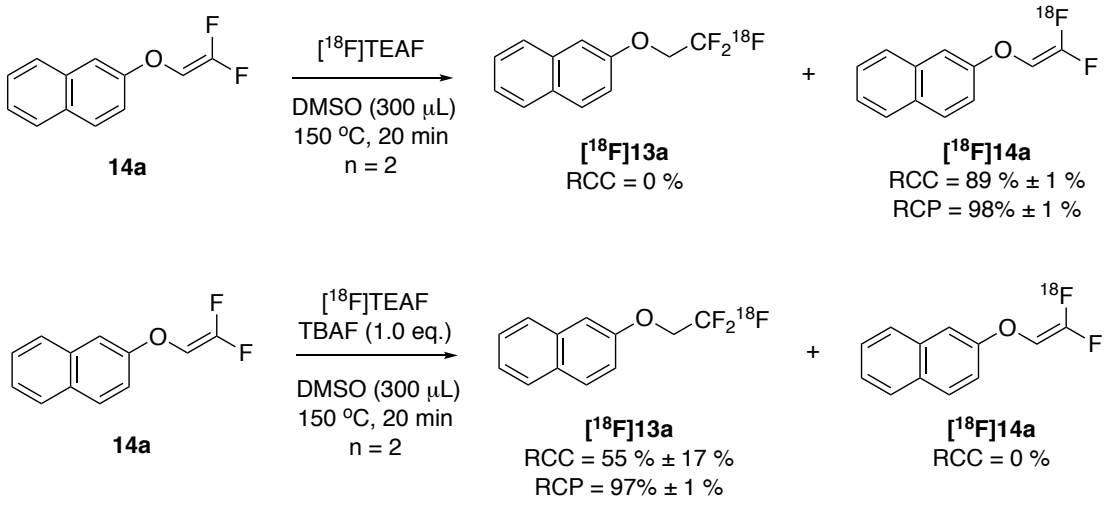
3.4 [^{18}F]H-F Addition across *gem*-difluoroenol ether

3.4.1 Carrier Added [^{18}F]H-F Addition across *gem*-difluoroenol ether

Labelling experiments in section **3.4.1** conducted at the Siemens Oxford Molecular Imaging Laboratory (SOMIL) by Thomas Wilson and Jeroen Sap.

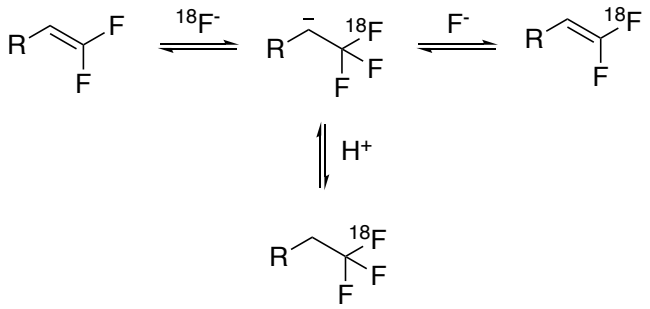
Net [^{18}F]HF addition across a *gem*-difluoroenol ether has only been successfully employed for the labelling of prosthetic groups – themselves used to generate the desired tracer. When this method was employed to label Lansoprazole directly, the desired tracer, [^{18}F]Lansoprazole, could only be generated as a 1:1 mixture with fluorine-18 labelled starting material, and with a very low RCY.

When *gem*-difluoroenol ether **14a** was exposed to non-carrier added conditions, only fluorine-18 labelled starting material was observed. However, when 1.0 equivalent of TBAF was present, the desired product was observed in 55 % RCC (± 17 %. n = 2).



Scheme 3.11 Radiolabelling the trifluoroethoxy motif with [^{18}F]TEAF.

The mechanism of net HF addition across a *gem*-difluoroalkene moiety is thought to proceed *via* an addition-elimination mechanism, with a carbanion intermediate. The carbanion stability is attributed to the adjoining trifluoromethyl moiety, and the charge stabilising ability of the adjacent functional group.[339-341,367] This short-lived intermediate is then trapped by a proton source to form the desired product – unfortunately in this case, intramolecular elimination outcompetes intermolecular proton capture (**Scheme 3.12**).



Scheme 3.12 Nucleophilic addition-elimination mechanism with [^{18}F]fluoride.

This method, although successfully allowing access to radiolabelled trifluoroethyl functionality **[^{18}F]13a**, inherently produces a vast excess of non-radiolabelled **13a –** leading to low specific activity. This method would therefore require large amounts of material to generate images of sufficient resolution. Attempts were consequently made to develop a non-carrier added approach to label the trifluoroethyl moiety.

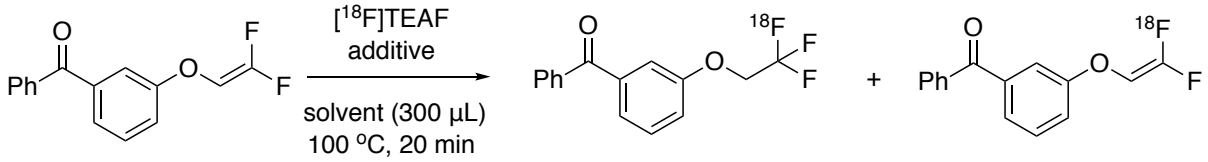
3.4.2 Non-Carrier Added [^{18}F]HF Addition across *gem*-difluoroenol ether

Labelling experiments in section **3.4.2** carried out by Rob Szpera, Dr. Natan Straathof and Dr. Patrick Isenegger.

The ratio of radiolabelled product to elimination product may be influenced by additives. Riss and co-workers observed that the equilibrium was highly dependent on residual water levels in the reaction solvent – anhydrous conditions favoured generation of the radiolabelled alkene, whereas water content of around 100 ppm generated the radiolabelled product exclusively, and water content of 1000 ppm or greater resulted in neither radiolabelled product.[343-345,368] Similarly, Scott and co-workers found the ratio of radiolabelled [^{18}F]Lansoprazole to radiolabelled alkene could be improved by the

addition of aliquots of isopropanol to the reaction vessel.[341] Hence, an additive screen was conducted (**Table 3.7**).

Table 3.7 Non-carrier added screening.



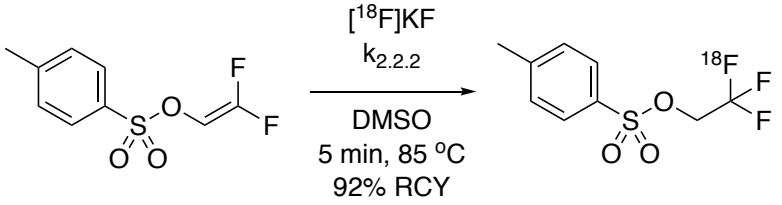
14h **[^{18}F]13h** **[^{18}F]14h**

Entry	Additive	Solvent	% TLC conv.	% HPLC purity [^{18}F]13h	% HPLC purity [^{18}F]14h	% RCC [^{18}F]13h
1	-	Wet DMSO	92	12	88	11
2	**TBAF.3H$_2$O (1 eq.)**	**Wet DMSO**	**57**	**98**	**2**	**56**
3	None	Dry DMSO	90	3	98	3
4	^{i}PrOH (1 eq.)	Dry DMSO	93	9	91	9
5	^{t}BuOH (1 eq.)	Dry DMSO	87	7	94	7
6	PPTS (1 eq.)	Dry DMSO	0	-	-	-
7	^{i}PrOH (100 eq.)	Dry DMSO	0	-	-	-
8[a]	-	THF	0	-	-	-
9	-	Diglyme	58	15	86	9
10	-	Dioxane	51	10	91	5
11	-	DMF	80	7	94	6
12	-	DME (dry)	91	12	89	11
13	-	DME, 1 vol% water	64	50	50	31
14	LiCl (1 eq.)	DME (2000)	0	-	-	-
15	$KHCO_3$ (1 eq.)	DME (2000)	82	29	72	24
16	$Et_4N.HCO_3$ (1 eq.)	DME (2000)	69	34	66	23
17	Dry off MeCN	DME, 1 vol% water	9	63	37	6

All reactions performed twice. Numerical values are the mean. **[a]** Reaction performed at 60 °C. **Procedure**: An aliquot of [^{18}F]TEAF (approx. 25 MBq) in MeCN was added to a V-vial (containing an additive where applicable). Substrate (0.03mmol) in wet DMSO (300 µL) was added and the vial was heated at 100 °C. The crude mixture was quenched by the addition of ethanol/water solution (9:1, 300 µL). An aliquot of the crude mixture was analysed by radio TLC and radio HPLC. **Water content of solvents**/ ppm (average measurement, n = 2); 'wet' DMSO = 2400; 'dry' DMSO = 35; THF = 676; diglyme – 364; dioxane = 186; DMF = 197; DME 'dry' = 117; DME 2000 = 2039.

Despite extensive additive and solvent screening, and variation of water content, radiochemical purity of desired product **[^{18}F]13h** could not be raised above 63 %. The short-lived intermediate carbanion is adjacent to lone pairs of electrons of the oxygen atom – in Riss's system, these lone pairs can be expected to have some resonance

delocalization into the sulfonate group.[343-345] This resonance can be theorised to impart sufficient stability to the intermediate carbanion to favour generation of the trifluoromethylated product.[341] In the system developed above, an aryl group is present – it is probable that the aryl group is unable to provide the same level of resonance delocalisation of the oxygen lone pairs and consequently gives much poorer carbanion stabilisation, resulting in a lower ratio of proton capture verses elimination.

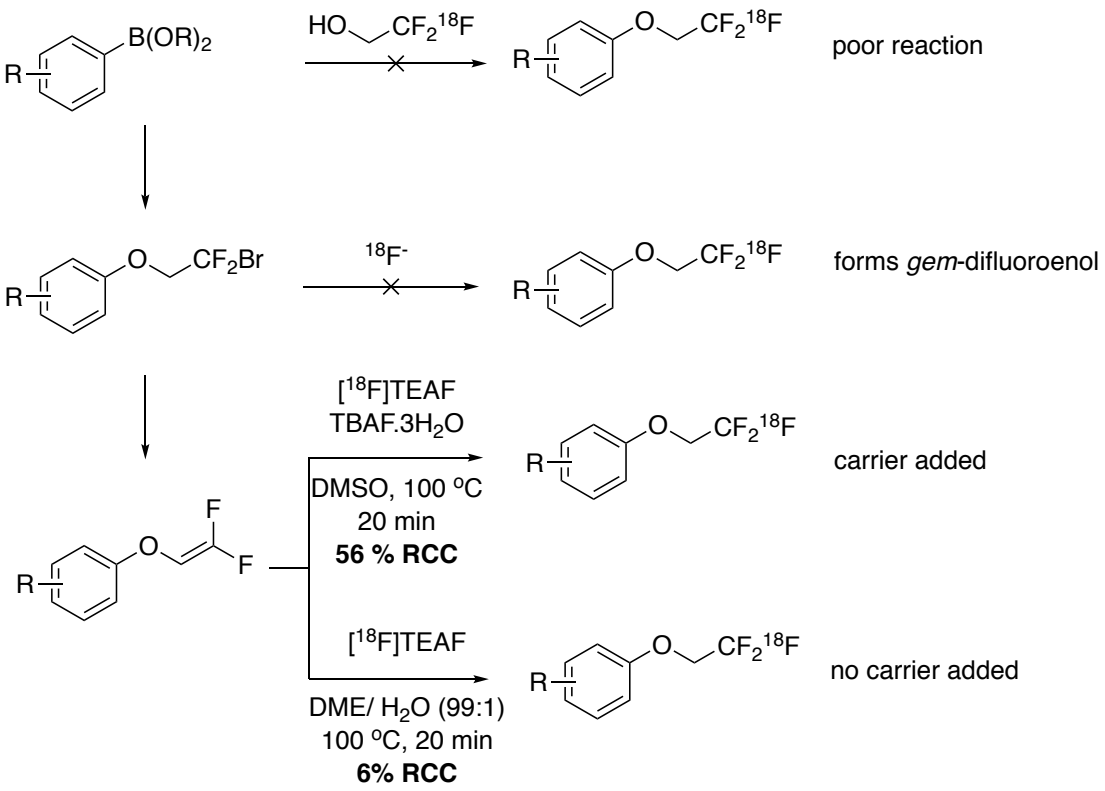


Scheme 3.13 Riss's net [^{18}F]HF addition across a *gem*-difluoroenol ether.

3.4.3 Radiolabelling Summary

In summary, three routes where probed for radiolabelling of the trifluoroethoxy motif: coupling of [^{18}F]trifluoroethanol with boronic ester species; ^{18}F/Br halogen exchange, and net [^{18}F]HF addition across a *gem*-difluoroenol ether. Direct coupling with [^{18}F]trifluoroethanol proved unfeasible as the cold reaction indicated that large excess of the boronate starting material – representative of radiochemical conditions – favoured the formation of side products over the desired product. ^{18}F/Br halogen exchange did not show any sign of proceeding, even in the presence of activating silver salts. Finally, net [^{18}F]HF addition across a *gem*-difluoroenol ether showed some sign of promise, giving good RCC and RCP of the desired radiolabelled product in carrier added mode. However, under non-carrier added conditions, suppression of unwanted addition-elimination

proved troublesome – with the best ratio of radiolabelled product to starting material being 2:1.



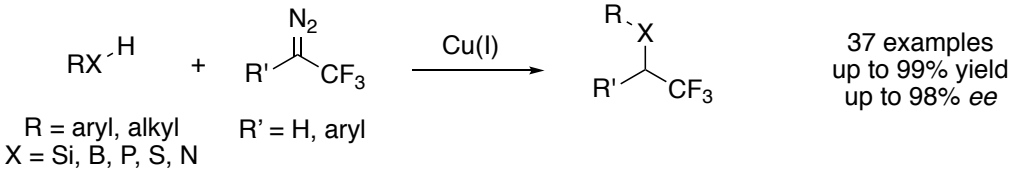
Scheme 3.14 Summary of radiolabelling of the trifluoroethoxy motif.

CONCLUSION

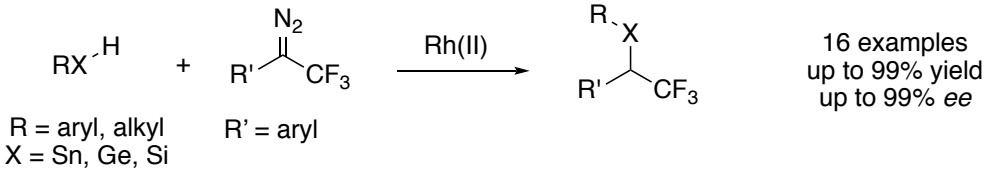
Conclusion

This thesis contributes three pieces of original work to the scientific community: a novel copper(I)-catalysed heteroatom-hydrogen bond insertion reaction; a rhodium(II)-catalysed heteroatom-hydrogen bond insertion reaction; and an exploration into novel ways of radiolabelling the trifluoroethoxy unit.

Copper(I)-Catalysed Heteroatom-Hydrogen Bond Insertion



Rhodium(II)-Catalysed Heteroatom-Hydrogen Bond Insertion



[^{18}F]-Radiolabelling of the Trifluoroethoxy Motif

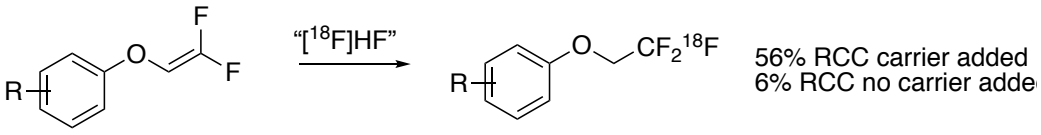


Figure C.1 Summary of Thesis.

The copper(I)-catalysed XHI reaction offers a significant contribution to synthetic methodology for accessing the heteroatom-trifluoroethyl motif, in non-substituted, α-substituted and asymmetric modes for a range of substrates: S-H, N-H, P-H, Si-H and B-H bonds. This methodology is exceptionally broad in its general utility to organic chemists for accessing highly desirable fluorinated scaffolds. The procedure is operationally simple, safe and economical in terms of stoichiometry; catalyst and ligand are both commercially available and loadings of both are low. The reaction times are

acceptable and deliver products in broadly good yields. Enantioselective variants of the transformation are attainable using this system for certain categories of substrate; generating exceptionally enantiopure material.

The rhodium(II)-catalysed XHI reaction is the first reported asymmetric Sn-H and Ge-H insertion reaction; the products of which may prove useful as trifluoromethylated organomatellic coupling partners, once systems are developed to supress beta-fluoride elimination during coupling processes.

The [^{18}F]trifluoroethoxy group the was labelled in 56 % RCC under carrier added conditions, and 6 % RCC under no carrier added conditions. This project involved the development of a novel coupling reaction of bromodifluoroethanol with boronic acid species under Chan-Lam conditions.

CHAPTER 4

Experimental Data

Chapter 4: Experimental Data

In this chapter, the full characterisation of compounds synthesised by S. Hyde is provided. The characterisation of compounds synthesised by Dr. B. Liégault, Dr. J. Veliks and Dr. D. Grassi, as well as spectra of novel compounds, may be found in the corresponding publications.[286]

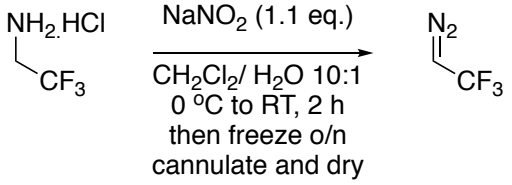
4.1 General Experimental Information

All solvents and chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Strem, Manchester Organics, Fluorochem or Apollo Scientific, and used without further purification, unless stated otherwise. All NMR spectra were recorded on Bruker DPX200, AV400 or AV500 spectrometers and are reported as chemical shifts (δ) in parts per million (ppm). ^{1}H NMR spectra are referenced relative to residual undeuterated solvent peak. ^{13}C NMR spectra referenced with respect to deuterated solvent peak. ^{19}F, ^{11}B and ^{31}P NMR spectra are referenced relative to $CFCl_3$, $BF_3 \bullet OEt_2$ and H_3PO_4, respectively. Coupling constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sept (septet), m (multiplet), br (broad). All NMR data was interpreted using iNMR software. High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using electrospray ionization (ESI) or on a Waters GCT TOF (temperature programmed solid's probe) using field ionisation (FI), electron ionisation (EI) or chemical ionisation (CI). Infrared spectra were recorded as neat compound using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks

of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. Thin layer chromatographies (TLC) were performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F_{254}. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography columns were performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment. ^{19}F NMR yields were obtained by integrating the product peak(s) relative to 1.0 equivalent of internal standard. Known compounds have been checked against literature references and only two pieces of analytical data are given.

4.2 Experimental Procedures and Characterisation Data for Chapter 2

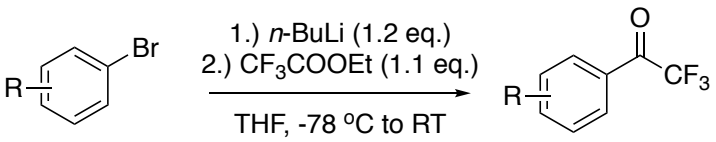
4.2.1 Preparation of 2-diazo-1,1,1-trifluoroethane 1a



Prepared according to adapted procedure from Carreira *et* al.[293] 2,2,2-Trifluoroethylamine hydrochloride (2.7 g, 20 mmol.) and $NaNO_2$ (1.5 g, 22 mmol.) were added to a round bottom flask equipped with a stir bar, and the flask was sealed with a septum and purged with argon three times. Degassed (three cycles of freeze-pump-thaw) dichloromethane (40 mL) was added under argon, and the reaction mixture, while stirring, was cooled to 0 °C. Degassed (by bubbling with argon for 30 minutes) H_2O (4 mL) was slowly added under argon. The solution was stirred for 2 h at 0 °C and then for an additional 1 hour at RT. The aqueous layer was frozen in the freezer (-18 °C, typically left for 12 to 18 h). The organic layer was then transferred using a Teflon needle to a flame-dried round bottom flask and dried (K_2CO_3,~ 5 g) for at least 1 h prior to use. An aliquot of the solution was taken to determine the concentration by ^{19}F NMR (according to an internal reference $PhCF_3$). Typically, 0.35-0.40 M solution of CF_3CHN_2 (**1a**) in CH_2Cl_2 was obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (q, $^3J_{HF}$ = 4.1). ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.2 (d, $^3J_{FH}$ = 4.0). Data consistent with literature values.[369]

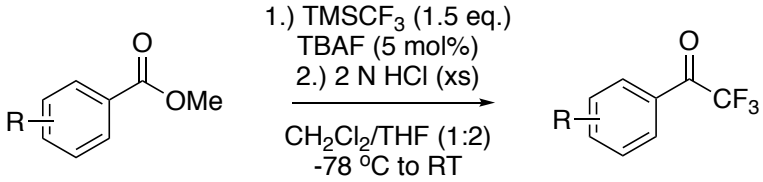
4.2.2 Preparation of Trifluoroacetophenones

General Procedure A



Procedure from Gouverneur *et al.*[273] To a solution of the desired aryl bromide (1.0 eq.) in THF (0.2 M) at -78 °C under argon was added *n*-BuLi (2.5 M in hexanes; 1.2 eq.) dropwise. After 1 hour at -78 °C, ethyl trifluoroacetate (1.1 eq.) was added dropwise *via* syringe. The solution was slowly warmed to room temperature overnight then quenched by slow addition of a saturated solution of NH_4Cl. The crude product was extracted with EtOAc, washed with water, brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography.

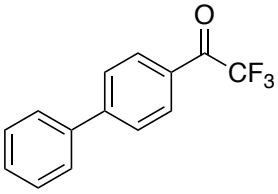
General Procedure B



Procedure from Olah *et al.*[370] To a stirred solution of methyl 4-benzoate (1.0 eq.) and $TMSCF_3$ (1.5 eq.) in CH_2Cl_2 (0.2 M) cooled to -78 °C was added TBAF dihydrate (1M in THF; 5 mol %). This mixture was then allowed to slowly warm to room temperature. After complete conversion of starting material (observed by TLC), 2M HCl (0.2 M) was added and the reaction mixture stirred for 18 h. Subsequently the organic phase was collected,

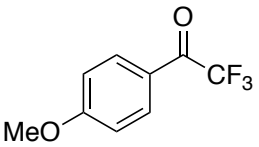
and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with saturated solutions of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography.

1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-one 1''b



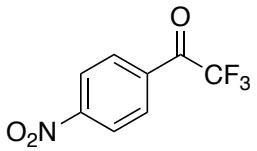
The title compound was prepared following general procedure A from 4-bromo-1,1'-biphenyl (9.32 g, 40 mmol). Used without further purification and obtained as a white solid (9.35 g, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 2H), 7.80-7.77 (m, 2H), 7.68-7.65 (m, 2H), 7.54-7.44 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4 (q, $^2J_{CF}$ = 35.1) 148.4, 139.3, 131.0, 129.4, 129.3, 128.9, 127.9, 127.6, 116.3 (q, $^1J_{CF}$ = 273). ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.3 (s). Data consistent with literature values.[371]

2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one 1''e



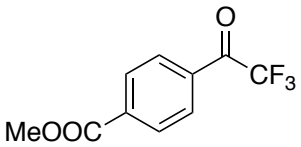
The title compound was prepared following general procedure A from 4-bromoanisole (1.87 g, 10 mmol) in THF (140 mL). Purified by silica gel column chromatography (petroleum ether/EtOAc 98:2) and obtained as a colourless oil (1.95 g, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.00 (d, $^3J_{HH}$ = 9.2, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9 (q, $^2J_{CF}$ = 34.8), 165.3, 132.6, 122.9, 114.5 (q $^1J_{CF}$ = 271), 114.3, 55.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.0 (s). Data consistent with literature values.[372]

2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-one 1''f



The title compound was prepared following general procedure B from methyl-4-nitrobenzoate (3.62 g, 20 mmol). Purified by silica gel column chromatography (petroleum ether/EtOAc 95:5) and obtained, as the hydrate, as a light yellow oil (1.87 g, 40 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 8.8, 2H), 7.95 (s, 2H, OH of hydrate), 7.85 (d, J = 8.8, 2H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -82.5 (s). Data consistent with literature values.[373]

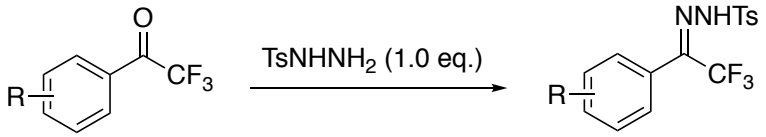
methyl 4-(2,2,2-trifluoroacetyl)benzoate 1''j



To a solution of 4-(2,2,2-trifluoroacetyl)benzoic acid (3.0 g, 13.8 mmol, 1 eq.) in methanol (60 ml) at room temperature was added concentrated sulfuric acid (800 µl) dropwise. The reaction mixture was heated to 60 °C for 15 hours then cooled to room temperature and neutralized with 1M NaOH. The solvent was removed under reduced pressure and the residue dissolved in EtOAc. The crude product was then washed with saturated solutions of $NaHCO_3$, water, and brine, dried with $MgSO_4$ and concentrated under reduced pressure to afford the title compound as an off-white solid (2.86 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $^{3}J_{HH}$ = 8.4, 2H), 7.12 (d, $^{3}J_{HH}$ = 8.4, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (q, $^{2}J_{CF}$ = 36.4), 165.2, 136.4, 133.4, 130.0, 129.9, 116.6 (q, $^{1}J_{CF}$ = 291), 53.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.5 (s). Data consistent with literature values.[374]

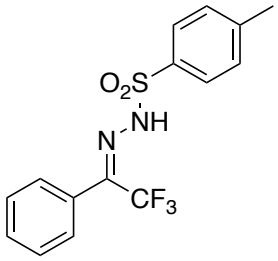
4.2.3 Preparation of Hydrazones

General Procedure C



Procedure from Wang *et al*.[279] To a round bottom flask surmounted with a reflux condenser was added tosylhydrazide (1.0 eq.) and the minimum quantity of solvent (either methanol or toluene according to individual substrates) needed to dissolve the hydrazide at reflux (approximately 1.5 M). Subsequently the reaction was cooled to room temperature and trifluoroacetophenone (1.0 eq.) was added in one portion. The reaction mixture was then stirred at 65 °C (MeOH) or 90 °C (Toluene) over 4-16 h (monitored by TLC). The solution was cooled to room temperature or 0 °C, at which point the product precipitated out of solution (precipitation can be induced by addition of pentane). The precipitate was collected by vacuum filtration and washed with pentane, in which case it was used without further purification. If no precipitation occurred, the solvent was removed under reduced pressure and the residue used in the next step without further purification. Hydrazone derivatives were found to be unstable on silica gel.

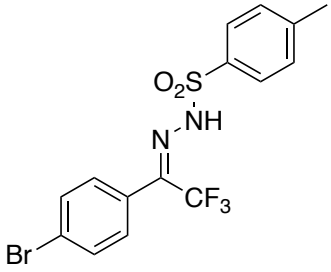
4-methyl-*N*'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide 1'd



The title compound was prepared following general procedure C from trifluoroacetophenone (2.09 g, 12 mmol.), in methanol (65 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (2.79 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H) 7.81 (m, 2H), 7.50 (m, 3H),

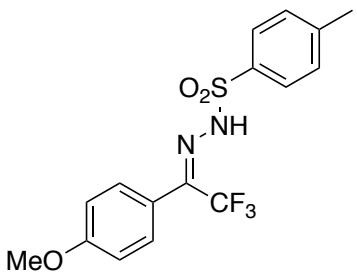
7.35 (d, $^{3}J_{HH}$ = 8.0, 2H), 7.25 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 141.4 (q, $^{2}J_{CF}$ = 35.7), 134.6, 130.1, 130.1, 128.3, 128.1, 125.3, 120.1 (q, $^{1}J_{CF}$ = 273), 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.2 (s). Data consistent literature values.[275]

_N_'-(1-(4-bromophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide



1'c The title compound was prepared following general procedure C from 4'-bromo-2,2,2-trifluoroacetophenone (2.43 g, 9.6 mmol.) in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (3.72 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H) 7.81 (m, 2H), 7.60 (m, 2H), 7.36 (d, $^{3}J_{HH}$ = 7.8, 2H), 7.15 (d, $^{3}J_{HH}$ = 7.8, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.5 (q, $^{2}J_{CF}$ = 36.0), 134.5, 133.7, 130.1, 130.0, 128.4, 126.8, 124.3, 120.0 (q, $^{1}J_{CF}$ = 273), 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.2 (s). Data consistent with literature values.[279]

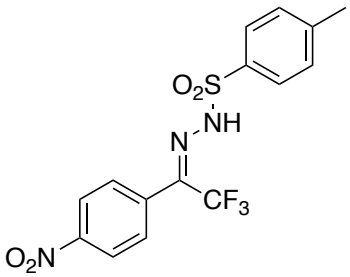
4-methyl-_N_'-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethylidene)benzenesulfonohydrazide 1'e



The title compound was prepared following general procedure C from 4'-methoxy-2,2,2-trifluoroacetophenone (4.08 g, 20 mmol.) in methanol (65 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as a pale yellow solid (2.31 g, 28%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.80-7.79 (m, 2H), 7.43 (m, 2H), 7.32-7.30 (m, 2H), 7.09-7.06 (m, 2H), 3.87 (s,

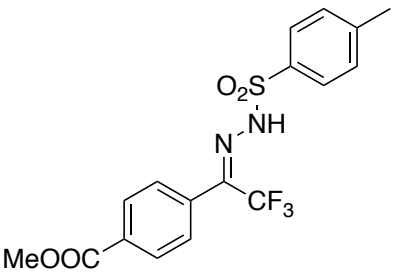
3H), 2.45 (s, 3H), (unable to see N-H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 144.1, 141.0 (q, $^{2}J_{CF}$ = 38.9), 135.3, 129.8, 129.2, 127.7, 120.4 (q, $^{1}J_{CF}$ = 274), 118.9, 114.2, 54.2, 20.0. ^{19}F NMR (376 MHz, CD_3OD) δ -65.5 (s). Data consistent with literature values.[273]

4-methyl-*N*'-(2,2,2-trifluoro-1-(4-nitrophenyl)ethylidene)benzenesulfonohydrazide 1'f



The title compound was prepared following general procedure C from 4'-nitro-2,2,2-trifluoroacetophenone (1.83 g, 8.37 mmol.) in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as a yellow solid (1.37 g, 42%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, $^{3}J_{HH}$ = 9.0, 2H), 7.80 (d, $^{3}J_{HH}$ = 8.4, 2H), 7.64 (d, $^{3}J_{HH}$ = 8.4, 2H), 7.44 (dd, $^{3}J_{HH}$ = 8.6, $^{4}J_{HH}$ = 0.7, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 149.1, 144.5, 138.2 (q, $^{2}J_{CF}$ = 38.9), 135.4, 133.1, 130.0, 129.3, 127.5, 124.0, 120.1 (q, $^{1}J_{CF}$ = 269.0), 20.0. ^{19}F NMR (376 MHz, CD_3OD) δ -69.4 (s). Data consistent with literature values.[273]

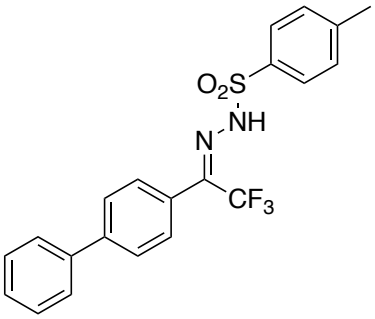
methyl-4-(2,2,2-trifluoro-1-(2-tosylhydrazineylidene)ethyl)benzoate 1'j



The title compound was prepared following general procedure C from corresponding trifluoroacetophenone (3.0 g, 12.9 mmol.) in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (4.36 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96, (s, 1H), 7.84 (m, 2H), 7.35 (m, 4H), 7.15 (d, 2H),

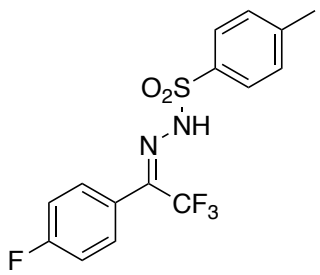
2.49 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 145.0, 140.4 (q, $^2J_{CF}$ = 36.5), 134.5, 133.2, 131.2, 130.0, 129.7, 128.6, 128.2, 120.0 (q, $^1J_{CF}$ = 273.0), 53.0, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.1 (s). Data consistent with literature values.[273]

_N_'-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide 1'b



The title compound was prepared following general procedure C from the corresponding trifluoroacetophenone (6.7 g, 36 mmol.), in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (11.4 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.84 (d, $^3J_{HH}$ = 8.3, 2H), 7.73 (d, $^3J_{HH}$ = 8.3, 2H), 7.60 (m, 2H), 7.50 (m, 2H), 7.43 (m, 1H), 7.35 (m, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.7, 141.6 (q, $^2J_{CF}$ = 35.7), 139.7, 134.7, 130.1, 129.3, 128.9, 128.8, 128.6, 128.2, 127.4, 124.0, 120.2 (q, $^1J_{CF}$ = 271), 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.1 (s). Data consistent with literature values.[371]

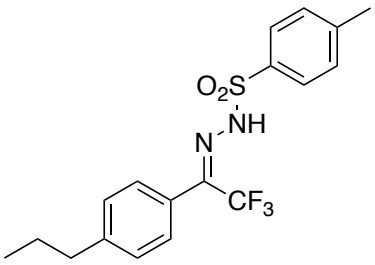
4-methyl-_N_'-(2,2,2-trifluoro-1-(4-fluorophenyl)ethylidene)benzenesulfonohydrazide



1'k The title compound was prepared following general procedure C from 2,2,2,4'-tetrafluoroacetophenone (1.0 g, 5.20 mmol.) in methanol (65 °C, 12 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (1.45 g, 77 %). Used without further purification.

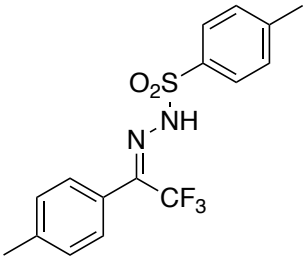
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.80 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 8.0, 2H), 7.29-7.19 (m, 4H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2 (d, $^{1}J_{CF}$ = 252.7), 145.2, 134.5, 130.9, 130.8, 130.0, 128.2, 120.1 (q, $^{1}J_{CF}$ = 274.9), 117.7, 117.5, 21.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ -68.36 (s, 3F), -106.50– -106.57 (m, 1F). Data consistent with literature values.[279]

4-methyl-*N*'-(2,2,2-trifluoro-1-(4-propylphenyl)ethylidene)benzenesulfonohydrazide



1'h The title compound was prepared following general procedure C from 4'-N-propyl-2,2,2-trifluoroacetophenone (1.0 g, 4.60 mmol.) in methanol (65 °C, 12 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (1.33 g, 75 %). Used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.81 (d, *J* = 8.3, 2H), 7.36-7.31 (m, 4H), 7.14 (d, *J* = 8.0, 2H), 2.63 (t, $^{3}J_{HH}$ = 7.7, 2H), 2.46 (s, 3H), 1.71-1.62 (m, 2H), 0.97 (t, $^{3}J_{HH}$ = 7.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.9, 145.0, 142.0 (q, $^{2}J_{CF}$ = 35.6), 134.7, 130.2, 130.0, 128.1, 122.5, 120.1 (q, $^{1}J_{CF}$ = 274.9), 77.2, 38.1, 24.3, 21.8, 14.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ -68.33 (s). M.p. 108-109 °C. IR (neat) υ/ cm^{-1}: 3171, 2964, 2924, 2857, 1359, 1170, 1119, 1070, 999, 811, 684. HRMS (ESI) calculated for $C_{18}H_{20}F_3N_2O_2S^+$ ($[M+H]^+$): 385.1192 observed: 385.1202.

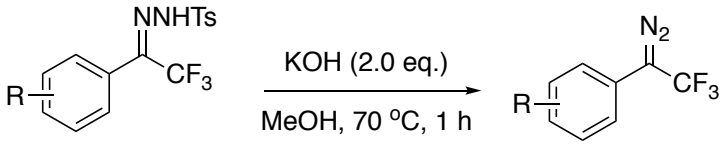
4-methyl-*N*'-(2,2,2-trifluoro-1-(*p*-tolyl)ethylidene)benzenesulfonohydrazide 1'g



The title compound was prepared following general procedure C from 2,2,2-trifluoro-1-(*p*-tolyl)ethan-1-one (1.0 g, 5.31 mmol.) in methanol (65 ^{o}C, 18 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (0.73 g, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H) 7.81 (d, $^{3}J_{HH}$ = 8.3, 2H), 7.32 (m, 4H), 7.13 (d, $^{3}J_{HH}$ = 8.3, 2H), 2.42 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 142.1, 141.8 (q, $^{2}J_{CF}$ = 35.8), 134.6, 130.7, 129.9, 128.0, 122.1, 119.0 (q, $^{1}J_{CF}$ = 275), 21.7, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.4. Data consistent with literature values.[279]

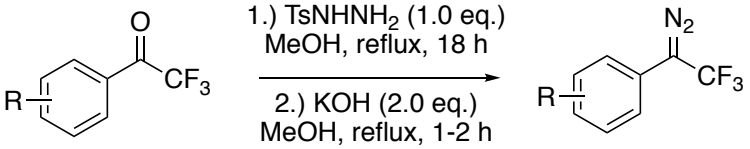
4.2.4 Preparation of Diazo Compounds

General Procedure D



Procedure from Xu *et al*.[375] Tosyl hydrazone (1.0 eq.) was heated at reflux in a solution of KOH (2 eq.) in MeOH (0.4 M) for 1 h or until the colour of the solution no longer intensified. The reaction was then cooled to room temperature and diluted with water. The crude product was extracted with CH_2Cl_2 or pentane (see individual substrates for details), washed with saturated solutions of $NaHCO_3$ and brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography. CAUTION: diazo compounds are presumed to be toxic and potentially explosive and should be handled with care, in a fume hood.

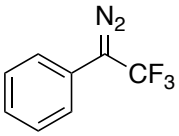
General Procedure E



To a mixture of tosyl hydrazine (1.0 eq.) in MeOH (1.5 M) was added ketone (1.0 eq). The reaction mixture was heated at reflux for 18 h then allowed to cool to room temperature. Solvent was evaporated under reduced pressure and the residue triturated with pentane, dried under vacuum and used in subsequent steps without additional purification. To the residue was added KOH (2.0 equiv.) in MeOH (0.4 M) and the reaction mixture heated to

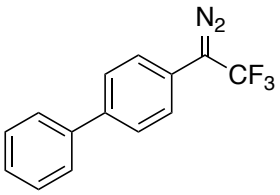
reflux for 1–2 hours, during which the characteristic red colour of diazo compounds appeared. The reaction mixture was cooled to room temperature, poured into water and extracted with pentane (x3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography.

(1-diazo-2,2,2-trifluoroethyl)benzene 1d



The title compound was prepared following general procedure D from tosylhydrazone 1'd (2.91 g, 8.5 mmol.). Purified by silica gel chromatography (pentane) and obtained as a volatile red liquid (544 mg, 35 %). CAUTION: diazo compounds are presumed to be toxic and potentially explosive and should be handled with care, in a fume hood. ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (m, 2H), 7.21 (m, 1H), 7.12 (d, $^{3}J_{HH}$ = 8.2, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 130.0, 126.7 (q, $^{1}J_{CF}$ = 269), 126.5, 123.9, 122.9 (C=N_2 not observed). ^{19}F NMR (376 MHz, C_6D_6) δ - 57.3 (s). Data consistent with literature values.[275]

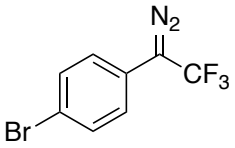
4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl 1b



The title compound was prepared following general procedure E from tosylhydrazone 1'b (7.41 g, 17.1 mmol). Purified by silica gel chromatography (pentane) and obtained as a orange/red solid (1.86 g, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.29 (m, 2H), 7.23 (m, 2H), 7.14 (m, 1H), 6.81 (d, $^{3}J_{HH}$ = 8.1, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.2, 128.0, 127.9,

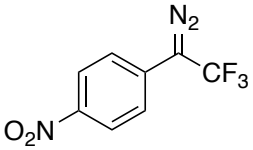
127.7, 127.6, 126.3 (q, $^{1}J_{CF}$ = 270), 125.6, 123.2, 122.1 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ - 57.4 (s). Data consistent with literature values.[371]

1-bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene 1c



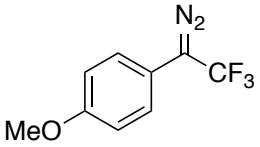
The title compound was prepared following general procedure D from tosylhydrazone 1'c (3.5 g, 8.3 mmol.). Purified by silica gel chromatography (pentane) and obtained as a deep red liquid (1.21 g, 55 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 6.97 (d, $^{3}J_{HH}$ = 8.6, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 125.7 (q, $^{1}J_{CF}$ = 270), 123.8, 122.9, 119.7 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6 (s). Data consistent with literature values.[273]

1-(1-diazo-2,2,2-trifluoroethyl)-4-nitrobenzene 1f



The title compound was prepared following general procedure D from tosylhydrazone 1'f (1.32 g, 3.4 mmol.). Purified by silica gel chromatography (pentane/CH_2Cl_2 90:10) and obtained as a yellow/ orange solid (465 mg, 60 %). ^{1}H NMR (500 MHz, C_6D_6) δ 7.65-7.65 (m, 2H), 6.25 (d, $^{3}J_{HH}$ = 8.9, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 145.0, 130.3, 124.2 (q, $^{1}J_{CF}$ = 270), 124.0, 121.0 (C=N_2 not observed). ^{19}F NMR (376 MHz, C_6D_6) δ -57.6 (s). Data consistent with literature values.[273]

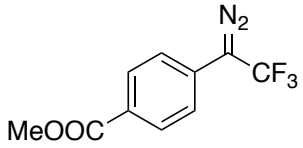
1-(1-diazo-2,2,2-trifluoroethyl)-4-methoxybenzene 1e



The title compound was prepared following general procedure D from tosylhydrazone 1'e (2.0 g, 5.38 mmol.). Purified by basic

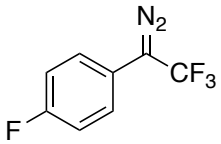
alumina gel chromatography (hexane) and obtained as a red solid (139 mg, 12 %). ^{1}H NMR (500 MHz, C_6D_6) δ 6.75-6.73 (m, 2H), 6.60 (d, $^{3}J_{HH}$ = 9.0, 2H), 3.21 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6 (s). Data consistent with literature values.[372]

methyl 4-(1-diazo-2,2,2-trifluoroethyl)benzoate 1j



The title compound was prepared following a modification of general procedure D: To a solution of tosylhydrazone 1'j (1.12 g, 2.8 mmol.) in MeOH (10 mL) was added NaOMe (303 mg, 5.6 mmol., 2 eq.). A condenser was attached and the reaction mixture refluxed for 1 h. The reaction was cooled to room temperature and diluted with water. The crude product was extracted with CH_2Cl_2, washed with saturated solutions of $NaHCO_3$ and brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography (pentane/CH_2Cl_2 90:10) and obtained as an orange solid (414 mg, 63 %). CAUTION: diazo compounds are presumed to be toxic and potentially explosive and should be handled with care, in a fume hood. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $^{3}J_{HH}$ = 8.8, 2H), 6.73 (d, $^{3}J_{HH}$ = 8.8, 2H), 3.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4, 126.3, 125.2 (q, $^{1}J_{CF}$ = 269.0), 124.1, 123.3, 122.5, 119.2 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.5 (s). Data consistent with literature values.[273]

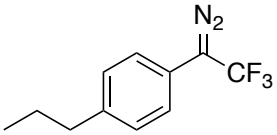
1-(1-diazo-2,2,2-trifluoroethyl)-4-fluorobenzene 1k



The title compound was prepared following general procedure D from tosylhydrazone 1'k (1.45 g, 4.0 mmol). Purified by silica gel chromatography (pentane) and obtained as a orange/red liquid (250 mg, 31 %). ^{1}H NMR

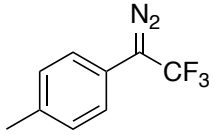
(400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7 (d, $^1J_{CF}$ = 246.8), 126.0 (q, $^1J_{CF}$ = 269.2), 124.4 (dq, *J* = 8.1, 1.4), 119.4 (d, *J* = 3.5), 116.8 (d, *J* = 22.3), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.55 (s, 3F), -115.91 (s, 1F). IR (neat) υ/ cm^{-1}: 3054, 2080, 1512, 1334, 1306, 1270, 1240, 1167, 1099, 957, 825, 735, 609. HRMS (ESI, negative) calculated for $C_8H_3F_4N_2^-$ ($[M-H]^-$): 203.0238 observed: 203.0233

1-(1-diazo-2,2,2-trifluoroethyl)-4-propylbenzene 1h



The title compound was prepared following general procedure D from tosylhydrazone 1'h (1.33 g, 3.46 mmol), purified by silica gel chromatography (pentane) and obtained as a orange/red liquid (194 mg, 25 %). ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, $^3J_{HH}$ = 8.6, 2H), 7.03 (d, $^3J_{HH}$ = 7.9, 2H), 2.60 (t, $^3J_{HH}$ = 7.6, 2H), 1.70-1.61 (m, 2H), 0.96 (t, $^3J_{HH}$ = 7.3, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -57.43 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 129.7, 125.7 (q, $^1J_{CF}$ = 268.6), 122.5, 120.5, 37.6, 24.6, 13.9, (C=N_2 not observed). IR (neat) υ/ cm^{-1}: 2963, 2934, 2874, 2079, 1516, 1345, 1276, 1167, 1145, 1105, 957, 835, 799, 738, 640. HRMS (ESI, negative) calculated for $C_{11}H_{10}F_3N_2^-$ ($[M-H]^-$): 227.0802 observed: 227.0556.

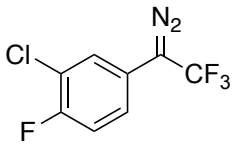
1-(1-diazo-2,2,2-trifluoroethyl)-4-methylbenzene 1g



The title compound was prepared following general procedure D from tosylhydrazone 1'g (0.72 g, 2.0 mmol), purified by silica gel chromatography (pentane) and obtained as a red liquid (169 mg, 42 %). ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.82 (d, $^3J_{HH}$ = 8.1, 2H), 6.75 (d, $^3J_{HH}$ = 8.1, 2H), 1.98 (s, 3H). ^{13}C NMR (126

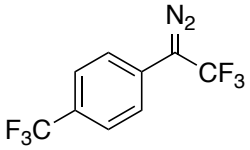
MHz, $CDCl_3$) δ 136.2, 130.7, 126.9 (q, $^1J_{CF}$ = 270), 123.1, 120.6, 60.2 (q, $^2J_{CF}$ = 43.9), 21.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.5 (s). Data consistent with literature values.[273]

2-chloro-4-(1-diazo-2,2,2-trifluoroethyl)-1-fluorobenzene 1n



The title compound was prepared following general procedure E from the corresponding trifluoroacetophenone (1.0 g, 4.4 mmol). Purified by silica gel column chromatography (pentane) and obtained as a red oil (14 mg, 2 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.6, 1H), 7.13 (dd, *J* = 6.4, 2.4, 1H), 6.98-6.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6 (d, $^1J_{CF}$ = 249.8), 126.7, 125.6 (q, $^1J_{CF}$ = 269.4), 124.6 (d, *J* = 1.3), 122.3 (m), 121.1 (d, *J* = 4.2), 117.9 (d, *J* = 22.0), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.47 (s, 3F), -118.14 (td, *J* = 7.2, 4.2, 1F). IR (neat) υ/ cm^{-1}: 2925, 2853, 2237, 2172, 2089, 2011, 1599, 1504, 1466, 1324, 1257, 1194, 1145, 1066, 814, 704, 628, 617. Compound 1n was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

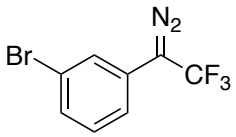
1-(1-diazo-2,2,2-trifluoroethyl)-4-(trifluoromethyl)benzene 1i



The title compound was prepared following general procedure E from 4'-trifluoromethyl-2,2,2-trifluoroacetophenone (1.01 g, 4.2 mmol.). Purified by silica gel column chromatography (pentane) and obtained as a yellow oil (46 mg, 4 % over two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73–7.50 (m, 2H), 7.22–7.07 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.3, 128.0 (q, $^2J_{CF}$ = 32.9), 126.5 (q, *J* = 3.9), 125.2 (q, $^1J_{CF}$ = 269.7), 124.0 (q, $^1J_{CF}$ = 271.8), 122.0 (d, *J* = 1.0), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.44 (s), -62.62 (s). IR (neat) υ/ cm^{-1}: 2931, 2859, 2088, 1619,

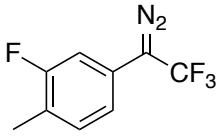
1523, 1325, 1280, 1206, 1169, 1110, 1069, 1016, 958, 831, 738. Compound 1i was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

1-bromo-3-(1-diazo-2,2,2-trifluoroethyl)benzene 1l



The title compound was prepared following general procedure E from 3'-bromo-2,2,2-trifluoroacetophenone (2.0 g, 7.9 mmol.). Purified by silica gel column chromatography (pentane) and obtained as a red oil (120 mg, 6 % over two steps). ^{1}H NMR (500 MHz, benzene-d_6): 7.02 – 6.88 (m, 2H), 6.55 (t, J = 7.9, 1H), 6.52 – 6.45 (m, 1H). ^{13}C NMR (125 MHz, benzene-d_6): δ 130.6, 128.7, 125.8, 125.5 (q, $^{1}J_{CF}$ = 269.3), 124.7, 123.5, 120.4, (C=N_2 not observed). ^{19}F NMR (471 MHz, benzene-d_6) δ -57.49 (s). IR (neat) υ/ cm^{-1}: 3071, 2082, 1594, 1561, 1481, 1349, 1324, 1261, 1172, 1106, 993, 968, 860, 773, 760, 710, 700, 678. Compound 1l was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

4-(1-diazo-2,2,2-trifluoroethyl)-2-fluoro-1-methylbenzene 1m

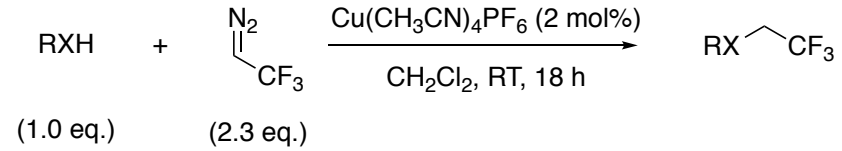


The title compound was prepared following general procedure E from the corresponding trifluoroacetophenone (1.8 g, 8.7 mmol.). Purified by silica gel column chromatography (pentane) and obtained as a red oil (47 mg, 2 % over two steps). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.24 (t, J = 8.2, 1H), 6.86 – 6.71 (m, 2H), 2.26 (d, $^{4}J_{HF}$ = 1.9, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 161.8 (d, $^{1}J_{CF}$ = 244.9), 132.5 (d, J = 6.2), 125.6 (q, $^{1}J_{CF}$ = 269.0), 122.8 (d, J = 9.1), 122.7 (d, J = 17.3), 117.7 (d, J = 3.2), 109.1 (d, J = 26.4), 61.8–59.1 (m), 13.8 (d, J = 3.5). ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.03

(s), -108.15– -119.66 (m). IR (neat) υ/ cm^{-1}: 2960, 2933, 2867, 2082, 1629, 1579, 1514, 1354, 1327, 1295, 1273, 1235, 1204, 1104, 1009, 875, 862, 807, 760, 734, 644. Compound 1m was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

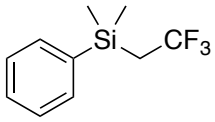
4.2.5 Copper-Catalysed Heteroatom-Hydrogen Bond Insertion with CF_3CHN_2

General Procedure F



Reactions were performed on a 0.3 mmol scale, unless otherwise specified. $Cu(CH_3CN)_4PF_6$ (2 mol%, 0.006 mmol, 2.2 mg) was placed into a vial and the substrate (0.3 mmol) also added at this point, if solid. The vial was purged with argon, then degassed CH_2Cl_2 (0.5 mL) was added. The substrate (0.3 mmol) was added at this point, if liquid. A solution of CF_3CHN_2 (**1a**) (2.3 equiv, 0.64 mmol, 2.0-2.6 mL) in CH_2Cl_2 (0.35-0.40 M) was then added at room temperature over 1 h with a syringe pump and the reaction mixture allowed to stir for 18 h (nitrogen evolution was monitored with an exhaust needle connected to an oil bubbler). Once the reaction was complete, the solvent was evaporated and the crude product directly loaded onto a silica gel chromatography column for purification.

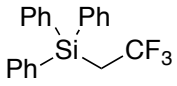
dimethyl(phenyl)(2,2,2-trifluoroethyl)silane 2aa



The title compound was prepared following general procedure F from dimethylphenylsilane. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (58 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.43-7.37 (m, 3H), 1.80 (q, $^3J_{HF}$ = 13.9, 2H), 0.45 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 133.6, 129.8, 128.4 (q, $^1J_{CF}$ = 274.4), 128.2, 23.9 (q, $^2J_{CF}$ = 29.1), -2.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.4 (t, $^3J_{FH}$ = 13.9). HRMS (FI) calculated for $C_{10}H_{13}F_3Si$

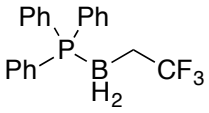
(M) 218.0739, observed: 218.0735. IR (neat) υ/ cm^{-1} 3073, 2964, 1414, 1278, 1248, 1216, 1088, 1030, 812, 727, 697, 639.

triphenyl(2,2,2-trifluoroethyl)silane 2ab



The title compound was prepared following general procedure F from triphenylsilane. Purified by silica gel column chromatography (pentane) and obtained as a white solid (79 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 6H), 7.49-7.44 (m, 3H), 7.42-7.38 (m, 6H), 2.46 (q, $^{3}J_{HF}$ = 13.3, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 132.6, 130.3, 128.2, 127.9 (q, $^{1}J_{CF}$ = 275.0), 22.4 (q, $^{2}J_{CF}$ = 29.3).^{19}F NMR (376 MHz, $CDCl_3$) δ -51.5 (t, $^{3}J_{FH}$ = 13.2). HRMS (FI) calculated for $C_{20}H_{17}F_3Si$ (M): 342.1052, observed: 342.1050. IR (neat) υ/ cm^{-1} 3062, 3021, 2922, 1487, 1279, 1112, 1083, 742, 732, 698. mp. 122-125 °C.

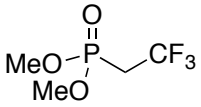
triphenylphosphine 2,2,2-trifluoroethylborane 5aa



The title compound was prepared following general procedure F from borane triphenylphosphine complex. Purified by silica gel column chromatography (pentane/CH_2Cl_2 9/1 to pentane/CH_2Cl_2 60/40) and obtained as an off-white solid (56 mg, 52 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.51 (m, 9H), 7.49-7.44 (m, 6H), 2.41-1.45 (br m, 2H), 1.44-1.27 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5 (d, J = 9.1), 131.7 (d, J = 2.4), 131.5 (qd, $^{1}J_{CF}$ = 275.2 and $^{3}J_{CP}$ = 22.4), 129.1 (d, J = 10.4), 127.6 (d, J = 57.3), 19.0 (m, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.0 (t, $^{3}J_{FH}$ = 13.7).^{11}B NMR (160 MHz, $CDCl_3$) δ -30.2 (m, 1B).^{31}P NMR (202 MHz, $CDCl_3$) δ 18.0 (d, J = 68). IR (neat) υ/ cm^{-1} 3062, 2951, 2925, 2376, 2288, 1436, 1290, 1261, 1239, 1105, 1067, 1012, 748, 691,

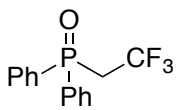
654. mp. 103-104 °C. Compound 5aa was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

dimethyl (2,2,2-trifluoroethyl)phosphonate 3ab



The title compound was prepared following an adaptation of general procedure F from dimethyl phosphite; the $Cu(CH_3CN)_4PF_6$ catalyst and co-catalytic amount of $NaBAr_F$ (2.2 mol%, 0.0066 mmol, 5.8 mg) were pre-stirred for 20 min in CH_2Cl_2 prior addition of substrate. Purified by silica gel column chromatography (CH_2Cl_2/MeOH 99/1 to 9/1 CH_2Cl_2/MeOH) and obtained as colourless oil (19 mg, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (d, $^3J_{HP}$ = 11.3, 6H), 2.76 (dq, $^2J_{HP}$ = 19.6 and $^3J_{HF}$ = 10.7, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.7 (qd, $^1J_{CF}$ = 275.7 and $^2J_{CP}$ = 3.1, CF_3), 53.3 (d, $^2J_{CP}$ = 6.2, OMe), 32.0 (dq, $^1J_{CP}$ = 144.1 and $^2J_{CF}$ = 31.5, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.6 (dt, $^3J_{FP}$ = 13.8 and $^3J_{FH}$ = 10.4). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.7 (q, $^3J_{PF}$ = 13.7). HRMS (FI) calculated for $C_4H_8F_3O_3P$ (M); 192.0163, observed: 192.0156. IR (neat) υ/ cm^{-1} 3487, 2965, 2933, 2861, 1321, 1260, 1238, 1124, 1025, 871, 797, 658.

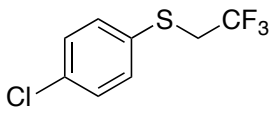
diphenyl(2,2,2-trifluoroethyl)phosphine oxide 3aa



The title compound was prepared following a modification of general procedure F from diphenylphosphine oxide; the $Cu(CH_3CN)_4PF_6$ catalyst and co-catalytic amount of $NaBAr_F$ (2.2 mol%, 0.0066 mmol, 5.8 mg) were pre-stirred for 20 min in CH_2Cl_2 prior addition of substrate. Purified by silica gel column chromatography (CH_2Cl_2/MeOH 99/1 to 95/5 CH_2Cl_2/MeOH) and obtained as a white solid (76 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 4H), 7.61-7.56 (m, 2H), 7.55-7.49 (m, 4H), 3.23

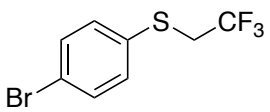
(dq, $^{2}J_{HP}$ = 11.9 and $^{3}J_{HF}$ = 10.6, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.7 (d, *J* = 2.8), 131.2 (d, *J* = 105.8), 131.0 (d, *J* = 9.7), 129.0 (d, *J* = 12.5), 124.2 (qd, $^{1}J_{CF}$ = 277.3, $^{2}J_{CP}$ = 4.1, CF_3), 36.9 (dq, $^{1}J_{CP}$ = 65.3, $^{2}J_{CF}$ = 29.2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.5 (td, $^{3}J_{FH}$ = 10.4 and $^{3}J_{FP}$ = 7.0). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.9 (q, $^{3}J_{PF}$ = 7.0). HRMS (FI) calculated for $C_{14}H_{12}F_3OP$ (M): 284.0578, observed: 284.0576. IR (neat) υ/ cm^{-1} 2960, 2197, 1439, 1313, 1272, 1244, 1193, 1119, 1062, 857, 835, 750, 721, 695. mp 142-144 °C.

(4-chlorophenyl)(2,2,2-trifluoroethyl)sulfane 4ae



The title compound was prepared following general procedure F from 4-chlorothiophenol. Purified by silica gel column chromatography (100 % pentane to 98/2 pentane/Et_2O) and obtained as a colourless oil (47 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, $^{3}J_{HH}$ = 8.5, 2H), 7.31 (d, $^{3}J_{HH}$ = 8.5, 2H), 3.41 (q, $^{3}J_{HF}$ = 9.6, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6, 133.5, 132.2, 129.6, 125.4 (q, $^{1}J_{CF}$ = 276.6), 38.44 (q, $^{2}J_{CF}$ = 32.8). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.3 (t, $^{3}J_{FH}$ = 9.7). HRMS (EI) calculated for $C_8H_6ClF_3S^+$ (M^+): 225.9825, observed: 225.9834. IR (neat) υ/ cm^{-1} 1575, 1308, 1240, 1122, 1076, 1012, 817, 637. Data consistent with literature values.[205]

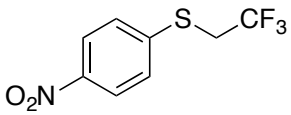
(4-bromophenyl)(2,2,2-trifluoroethyl)sulfane 4af



The title compound was prepared following general procedure F from 4-bromothiophenol. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (70 mg, 86 %). ^{1}H NMR (500 MHz, CD_3CN) δ 7.55-7.48 (m, 2H), 7.44-7.38 (m, 2H), 3.66 (q, $^{3}J_{HF}$ = 10.0, 2H). ^{13}C

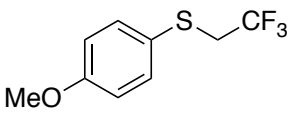
NMR (126 MHz, CD_3CN) δ 134.1, 133.5, 133.2, 126.8 (q, $^1J_{CF}$ = 275.7), 122.2, 37.2 (q, $^2J_{CF}$ = 32.4). ^{19}F NMR (377 MHz, CD_3CN) δ -67.0 (t, $^3J_{FH}$ = 10.2). HRMS (CI) calculated for $C_8H_6BrF_3S^+$ (M^+): 269.9326, observed: 269.9333. IR (neat) υ/ cm^{-1} 3061, 3092, 2359, 2262, 1246, 1128, 1082, 832. Data consistent with literature values.[376]

(4-nitrophenyl)(2,2,2-trifluoroethyl)sulfane 4ad



The title compound was prepared following general procedure F from 4-nitrothiophenol. Purified by silica gel column chromatography (92/8 pentane/ether) and obtained as a yellow solid (62 mg, 87 %). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21–8.18 (m, 2H), 7.55–7.51 (m, 2H), 3.61 (q, $^3J_{HF}$ = 9.4, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.8, 143.2, 129.0, 125.0 (q, $^1J_{CF}$ = 276.7), 124.4, 36.1 (q, = $^2J_{CF}$ = 33.8). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.06 (t, $^3J_{FH}$ = 9.5). HRMS (CI) calculated for $C_8H_{10}F_3N_2O_2S^+$ ($M+NH_4^+$): 255.0415, observed: 255.0412. IR (neat) υ/ cm^{-1} 3099, 2359, 2262, 1518, 1341, 1242, 1130, 1080. mp 42-43 °C. Data consistent with literature values.[377]

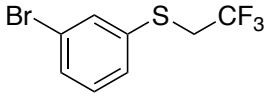
(4-methoxyphenyl)(2,2,2-trifluoroethyl)sulfane 4ac



The title compound was prepared following general procedure F from 4-methoxythiophenol. Purified by silica gel column chromatography (95/5 pentane/ether) and obtained as a colourless oil (64 mg, 90 %). ^1H NMR (400 MHz, CD_3CN) δ 7.76-7.12 (m, 2H), 7.12-6.65 (m, 2H), 3.78 (s, 3H), 3.51 (q, $^3J_{HF}$ = 10.2, 2H). ^{13}C NMR (377 MHz, CD_3CN) δ 161.1, 135.6, 127.1 (q, $^1J_{CF}$ = 275.6),

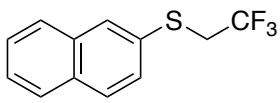
124.7, 115.8, 56.1, 39.1 (q, $^{2}J_{CF}$ = 31.7). ^{19}F NMR (377 MHz, CD_3CN) δ -67.0 (t, $^{3}J_{FH}$ = 10.4). HRMS (CI) calculated for $C_9H_9F_3OS^+$ (M^+): 222.0326, observed: 222.0335. IR (neat) υ/ cm^{-1} 3656, 2262, 1245, 1124, 1082, 1030, 832. Data consistent with literature values.[378]

(3-bromophenyl)(2,2,2-trifluoroethyl)sulfane 4ag



The title compound was prepared following general procedure F from 3-bromoxythiophenol. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (60 mg, 74 %). ^{1}H NMR (400 MHz, CD_3CN) δ 7.68 (t, *J* = 1.9, 1H), 7.46 (ddq, *J* = 8.1, 2.2, 1.0, 2H), 7.27 (t, *J* = 7.9, 1H), 3.69 (q, $^{3}J_{HF}$ = 10.0, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 136.70, 133.20, 131.44, 131.13, 129.76, 126.36 (q, $^{1}J_{CF}$ = 275.6), 122.91, 36.49 (q, $^{2}J_{CF}$ = 32.6). ^{19}F NMR (377 MHz, CD_3CN) δ -67.0 (t, $^{3}J_{FH}$ = 10.0). HRMS (CI) calculated for $C_8H_6BrF_3S^+$ (M^+): 269.9326, observed: 269.9313. IR (neat) υ/ cm^{-1} 3058, 1574, 1460, 1308, 1240, 1123, 1077. Data consistent with literature values.[379]

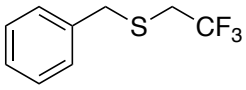
naphthalen-2-yl(2,2,2-trifluoroethyl)sulfane 4ab



The title compound was prepared following general procedure F from 2-naphthalenethiol. Purified by silica gel column chromatography (100 % pentane to 99/1 pentane/ether) and obtained as a colourless oil (58 mg, 79 %). ^{1}H NMR (400 MHz, CD_3CN) δ 8.05 (s, 1H), 7.92-7.86 (m, 3H), 7.60-7.54 (m, 3H), 3.81 (q, $^{3}J_{HF}$ = 10, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 134.6, 133.3, 132.0, 130.3, 129.9,

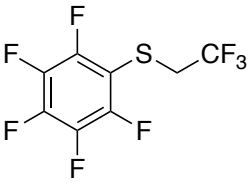
128.8, 128.7, 128.3, 127.9, 127.6, 127.0 (q, $^{1}J_{CF}$ = 275.5), 37.2 (q, $^{2}J_{CF}$ = 32.3). ^{19}F NMR (377 MHz, CD_3CN) δ -66.9 (t, $^{3}J_{FH}$ = 9.5). HRMS (CI) calculated for $C_{12}H_9F_3S^+$ (M^+): 242.0377, observed: 242.0379. IR (neat) υ/ cm^{-1} 3057, 2360, 2341, 2282, 1310, 1242, 1124, 1082.

benzyl(2,2,2-trifluoroethyl)sulfane 4aa



The title compound was prepared following general procedure F from benzyl mercaptan. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (48 mg, 78 %). ^{1}H NMR (400 MHz, CD_3CN) δ 7.40-7.34 (m, 5H), 3.91 (s, 2H), 3.13 (t, $^{3}J_{HF}$ = 10.4, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 138.2, 130.1, 129.7, 128.4, 127.6 (q, $^{1}J_{CF}$ = 275.4), 37.3, 33.6 (q, $^{2}J_{CF}$ = 32.3). ^{19}F NMR (377 MHz, CD_3CN) δ -66.7 (t, $^{3}J_{FH}$ = 10.4). IR (neat) υ/ cm^{-1} 3031, 2364, 1310, 1270, 1120, 1080. Data consistent with literature values.[380]

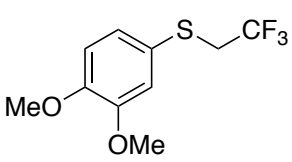
(perfluorophenyl)(2,2,2-trifluoroethyl)sulfane 4aj



The title compound was prepared following general procedure F from 2,3,4,5,6-Pentafluorothiophenol. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (20 mg, 24 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (q, $^{3}J_{HF}$ = 9.2, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7 (ddq, J_{CF} = 247.6, 10.3, 4.0), 142.4 (dtt, J_{CF} = 257.7, 13.5, 5.0), 139.0-136.6 (m), 124.6 (q, $^{1}J_{CF}$ = 276.7), 106.6 (td, J_{CF} = 20.5, 4.6), 36.5 (q, $^{2}J_{CF}$ = 33.7). ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.1 (t, $^{3}J_{FH}$ = 9.0, 3F), -131.9 (d, J_{FF} = 17.5,

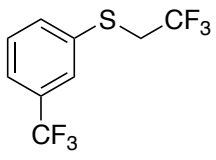
2F), -150.1 (t, J_{FF} = 20.9, 1F), -160.0– -160.2 (m, 2F). HRMS (EI) Calculated for $C_8H_2F_8S^+$ (M^+) 281.9749, Found 281.9754. IR (neat) υ/ cm^{-1} 2925, 2884, 2360, 2341, 1748, 1491, 1244, 1178, 1095, 983, 668, 655.

(3,4-dimethoxyphenyl)(2,2,2-trifluoroethyl)sulfane 4ak



The title compound was prepared following general procedure F from 3,4-dimethoxythiophenol. Purified by silica gel column chromatography (CH_2Cl_2) and obtained as a colourless oil (42 mg, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 8.3, 2.1, 1H), 7.05 (d, J = 2.1, 1H), 6.81 (d, J = 8.3, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.34 (q, $^3J_{HF}$ = 9.8, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 149.1, 126.7, 125.5 (q, $^1J_{CF}$ = 270.7), 124.3, 116.6, 111.5, 56.0, 55.9, 39.6 (q, $^2J_{CF}$ = 32.1). ^{19}F NMR (377 MHz, $CDCl_3$) δ -66.3 (t, $^3J_{FH}$ = 9.6, 3F). HRMS (EI) Calculated for $C_{10}H_{11}F_3O_2S^+$ (M^+) 252.0432, Found 252.0436. IR (neat) υ/ cm^{-1} 2999, 2955, 2013, 2841, 1503, 1307, 1250, 1229, 1178, 1117, 1077, 1023, 839, 804, 763, 605.

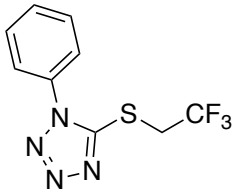
(2,2,2-trifluoroethyl)(3-(trifluoromethyl)phenyl)sulfane 4al



The title compound was prepared following general procedure F from3-(trifluoromethyl)thiophenol. Purified by silica gel column chromatography (pentane) and obtained as a yellow oil (17 mg, 22 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.66 (d, J = 8.0, 1H), 7.56 (d, J = 7.6, 1H), 7.47 (t, J = 7.9, 1H), 3.48 (q, $^3J_{HF}$ = 9.5, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0, 134.7, 131.8 (q, $^2J_{CF}$ = 32.7), 129.7,

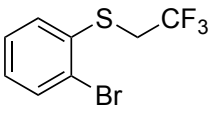
128.1 (q, $^{3}J_{CF}$ = 3.7), 125.1 (q, $^{1}J_{CF}$ = 276.6), 124.8 (q, $^{3}J_{CF}$ = 3.7), 123.5 (q, $^{1}J_{CF}$ = 272.7), 37.7 (q, $^{2}J_{CF}$ = 33.0). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s, 3F), -66.3 (t, $^{3}J_{FH}$ = 9.5, 3F). HRMS (EI) Calculated for $C_9H_6F_6S^+$ (M^+) 260.0094, Found 260.0095. IR (neat) υ/ cm^{-1} 2956, 2925, 2855, 2361, 2341, 1732, 1459, 1323, 1262, 1244, 1173, 1133, 798, 696, 669.

1-phenyl-5-((2,2,2-trifluoroethyl)thio)-1*H*-tetrazole 4ai



The title compound was prepared following general procedure F from 1-phenyl-1*H*-tetrazole-5-thiol. Purified by silica gel column chromatography (100 % dichloromethane) and obtained as a yellow oil (45 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.53 (m, 5H), 4.15 (q, $^{3}J_{HF}$ = 9.4, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9, 133.1, 130.7, 130.1, 124.2 (q, $^{1}J_{CF}$ = 276.6), 124.0, 34.8 (q, $^{2}J_{CF}$ = 34.9). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.7 (t, $^{3}J_{HF}$ = 9.2). HRMS (ESI) calculated for $C_9H_8F_3N_4S^+$ ($M+H^+$): 261.0416, observed: 261.0416. IR (neat) υ/ cm^{-1} 3011, 2960, 1597, 1500, 1392, 1315, 1272, 1240, 1134, 1088, 1015, 843, 760, 687, 638. Data consistent with literature values.[381]

(2-bromophenyl)(2,2,2-trifluoroethyl)sulfane 4ah

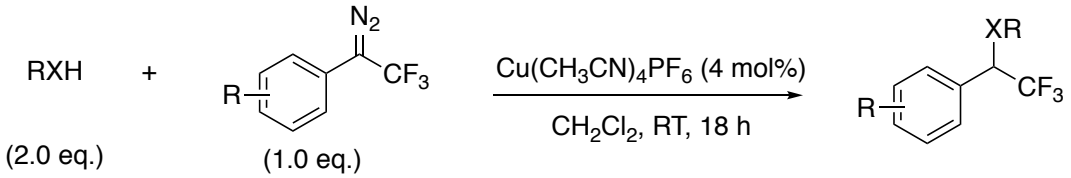


The title compound was prepared following general procedure F from 2-bromothiophenol. Purified by silica gel column chromatography (pentane/EtOAc 95:5) and obtained as a colourless oil (28 mg, 34 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9, 1H), 7.55 (d, *J* = 7.6, 1H), 7.30 (t, *J* = 7.3, 1H), 7.17 (t, *J* = 7.2, 1H), 3.49 (q, $^{3}J_{HF}$ = 9.6, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1, 133.5, 133.0, 129.4, 128.1, 126.8, 125.3 (q, $^{1}J_{CF}$ = 276.7), 36.7 (q, $^{2}J_{CF}$ = 32.9). ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.8 (t,

$^{3}J_{FH}$ = 9.7, F). HRMS (EI) calculated for $C_8H_6BrF_3S^+$ (M^+): 269.9326, observed: 269.9333. IR (neat) υ/ cm^{-1} 3060, 2925, 2854, 2360, 2341, 1750, 1446, 1308, 1241, 1122, 1111, 1080, 1019, 747. Data consistent with literature values.[382]

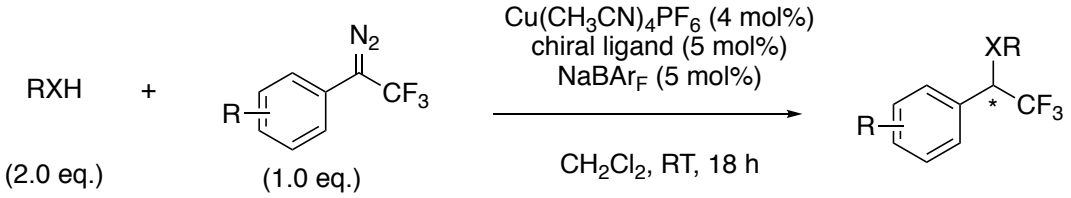
4.2.6 Copper-Catalysed Heteroatom-Hydrogen Bond Insertion with $CF_3C(Ar)N_2$

General Procedure G



Reactions were performed on 0.1 mmol scale, unless otherwise specified. $Cu(CH_3CN)_4PF_6$ (4.0 mol%, 1.5 mg) was placed into a vial. The substrate (0.2 mmol, 2.0 eq.) was also added at this point, if solid. The vial was purged with argon, then degassed CH_2Cl_2 (0.5 mL) was added. The substrate (0.2 mmol, 2.0 eq.) was added at this point, if liquid. A solution of the $CF_3C(Ar)N_2$ (1.0 eq.) in CH_2Cl_2 (0.8 mL) was then added at room temperature over 1 h with a syringe pump and the reaction mixture allowed to stir for 18 h (nitrogen evolution was monitored with an exhaust needle connected to an oil bubbler). Once the reaction was complete, the solvent was evaporated and the crude product directly loaded onto a silica gel chromatography column for purification.

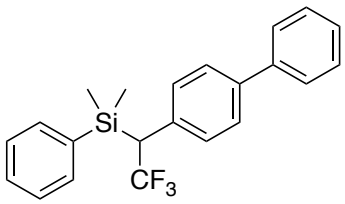
General Procedure H



Reactions were performed on a 0.1 mmol scale, unless otherwise specified. $Cu(CH_3CN)_4PF_6$ (4.0 mol% 1.5 mg), $NaBAr_F$ (5 mol%, 0.005 mmol, 5.3 mg) and the chiral ligand (5 mol%, 0.005 mmol) were placed into a vial. The vial was purged with argon,

degassed CH_2Cl_2 (0.5 mL) was added and the solution was stirred at room temperature for 2 h. The substrate (2 eq., 0.2 mmol) was then added, followed by a solution of the $CF_3CH(Ar)N_2$ reagent (1 eq.) in CH_2Cl_2 (0.7 mL) over 1 hour with a syringe pump (nitrogen evolution was monitored with an exhaust needle connected to an oil bubbler). Once the reaction was complete, the solvent was evaporated and the crude product directly loaded onto a silica gel chromatography column for purification. The enantiomeric excess of purified product was determined by HPLC analysis using a chiral stationary phase.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane 2ba

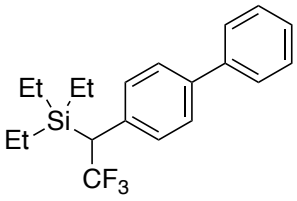


The title compound was prepared following general procedure G on a 0.3 mmol scale from dimethylphenylsilane and diazo compound 1b. Purified by silica gel column chromatography (pentane/CH_2Cl_2 95/5 to pentane/CH_2Cl_2 85/15) and obtained as a colourless oil (109 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.3, 2H), 7.49-7.41 (m, 4H), 7.40-7.30 (m, 6H), 7.06 (d, J = 8.1, 2H), 3.16 (q, $^3J_{HF}$ = 12.9, 1H), 0.48 (s, 3H), 0.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 139.5, 135.3, 134.3, 132.9 (q, J = 3.2), 129.8, 129.5, 128.9, 128.3 (q, $^1J_{CF}$ = 277.7, CF_3), 127.9, 127.4, 127.1, 127.1, 43.8 (q, $^2J_{CF}$ = 27.7), -3.4, -3.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.5 (d, $^3J_{FH}$ = 13.0). HRMS (EI) calculated for $C_{22}H_{21}F_3Si^+$ (M^+): 370.1359, observed: 370.1363. IR (neat) υ/ cm^{-1} 3071, 3031, 2963, 2905, 2362, 2284, 1488, 1239, 1151, 1133, 1068, 810, 764, 739, 695, 649.

Asymmetric reaction was performed using general procedure **H**, diazo **1b** and ligand L8**.** The product **(*R*)-2ba** was obtained in 99 % yield and 98 % *ee* [HPLC conditions; Chiralcel

OJ-H column, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min, 25 °C, wavelength = 250 nm, t_R = 14.93 min for minor isomer, t_R = 19.51 min for major isomer: $[\alpha]_D^{25}$ = -60.2 (*c* 1.10, MeOH).

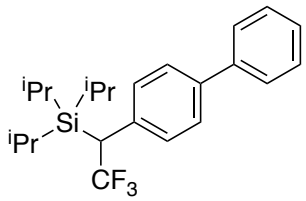
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triethylsilane 2bb



The title compound was prepared following general procedure G on a 0.1 mmol scale from triethylsilane and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (25 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.54-7.52 (m, 2H), 7.44-7.40 (m, 2H), 7.35-7.31 (m, 1H), 7.25 (d, *J* = 8.7, 2H), 3.05 (q, $^3J_{HF}$ = 13.2, 1H), 0.93 (t, $^3J_{HH}$ = 7.9, 9H), 0.73-0.59 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 139.4, 133.3 (q, = 3.4), 129.4, 128.8, 128.4 (q, $^1J_{CF}$ = 277.4), 127.3, 127.2, 126.9, 40.5 (q, $^2J_{CF}$ = 28.2), 7.1, 2.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.76 (d, $^3J_{FH}$ = 13.2, 3F). HRMS (CI) calculated for $C_{20}H_{29}F_3NSi^+$ ($M+NH_4^+$): 368.2016, observed: 368.2010. IR (neat) υ/ cm^{-1} 695, 713, 1007, 1070, 1123, 1152, 1244, 2879, 2956.

Asymmetric reaction was performed using general procedure **H**, diazo **1b** and ligand L8**.** The product (*R*)-**2bb** was obtained in 80 % yield and 98 % *ee* [HPLC conditions; Chiralpak IA column, hexane 100 %, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 7.16 min for minor isomer, t_R = 7.53 min for major isomer: $[\alpha]_D^{25}$ = -61.1 (*c* 1.30, MeOH).

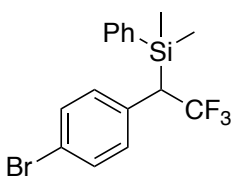
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triisopropylsilane 2bc



The title compound was prepared following general procedure G on a 0.1 mmol scale from triisopropylsilane and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (24 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.3, 2H), 7.55 (d, *J* = 8.3, 2H), 7.44 (t, *J* = 7.6, 2H), 7.35 (m, 3H), 3.28 (q, $^{3}J_{HF}$ = 13.4, 1H), 1.27-1.25 (m, 3H), 1.11 (d, $^{3}J_{HH}$ = 7.3, 9H), 1.02 (d, $^{3}J_{HH}$ = 7.4, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 139.6, 133.5 (q, *J* = 3.4), 130.7, 128.8, 128.5 (q, $^{1}J_{CF}$ = 277.5), 127.3, 127.1, 126.9, 39.3 (q, $^{2}J_{CF}$ = 28.3), 18.7, 11.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.12 (d, $^{3}J_{FH}$ = 13.4, 3F). HRMS (CI) calculated for $C_{23}H_{35}F_3NSi^+$ ($M+NH_4^+$): 410.2485, observed: 410.2489. IR (neat) υ/ cm^{-1} 3726, 2948, 2870, 2360, 2341, 1240, 1134, 1074.

Asymmetric reaction was performed using general procedure H, diazo **1b** and ligand L8**.** The product (-)-**2bc** was obtained in 68 % yield and 17 % *ee* [HPLC conditions; Chiralpak IA column, hexane 100 %, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 6.76 min for minor isomer, t_R = 7.26 min for major isomer: $[\alpha]_D^{25}$ = -8.1 (*c* 0.65, MeOH).

(1-(4-bromophenyl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane 2ca

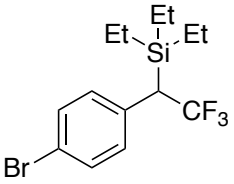


The title compound was prepared following general procedure G on a 0.1 mmol scale from dimethylphenylsilane and diazo compound 1c. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (25 mg, 67 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.37 (m, 1H), 7.36-7.30 (m, 6H), 6.84 (d, *J* = 8.3, 2H), 3.07 (q, $^{3}J_{HF}$ = 12.8, 1H), 0.44 (s, 3H), 0.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8, 134.3, 132.9 (q, *J* = 3.3), 131.6, 130.7, 130.0, 127.9 (q, $^{1}J_{CF}$ = 277.6), 127.9, 120.7, 43.7 (q, $^{2}J_{CF}$ = 28.0), -3.5, -3.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ -56.66 (d, $^{3}J_{FH}$ = 12.5). HRMS (CI) calculated for $C_{16}H_{20}BrF_3NSi^+$ ($M+NH_4^+$): 392.0480, observed: 392.0471. IR (neat) υ/ cm^{-1} 3072, 3051, 3028, 2963, 2905, 1590, 1490, 1429 1411, 1337, 1303, 1241, 1199, 1154, 1133, 1116, 1074, 1011, 889, 837, 811, 784, 739, 726, 698, 650.

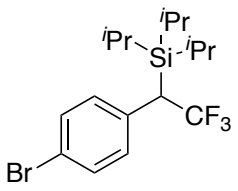
Asymmetric reaction was performed using general procedure **H**, diazo **1c** and ligand L8**.** The product (-)-**2ca** was obtained in 75 % yield with this procedure. 98 % *ee* [HPLC conditions; Chiralcel OD-H column, hexane/*i*-PrOH = 99.5:0.5, flow rate = 0.5 mL/min, 25 °C, wavelength = 225 nm, t_R = 11.28 min for minor isomer, t_R = 11.68 min for major isomer: $[\alpha]_D^{25}$ = -67.8 (*c* 1.25, MeOH).

(1-(4-bromophenyl)-2,2,2-trifluoroethyl)triethylsilane 2cb



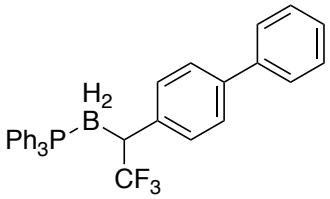
The title compound was prepared following general procedure G on a 0.1 mmol scale from triethylsilane and diazo compound 1c. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (27 mg, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, $^{3}J_{HH}$ = 8.6, 2H), 7.07 (d, $^{3}J_{HH}$ = 8.2, 2H), 2.98 (q, $^{3}J_{HF}$ = 13.1, 1H), 0.92 (t, $^{3}J_{HH}$ = 7.9, 9H), 0.72 – 0.52 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.6 (q, *J* = 3.5), 131.8, 130.8, 128.2 (q, $^{1}J_{CF}$ = 277.3), 120.7, 40.5 (q, $^{2}J_{CF}$ = 28.5), 7.20, 3.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.0 (d, $^{3}J_{FH}$ = 13.0). HRMS (CI) calculated for $C_{14}H_{24}BrF_3NSi^+$ ($M+NH_4^+$): 372.0793, observed: 372.0755. IR (neat) υ/ cm^{-1} 2948, 2871, 1490, 1465, 1409, 1388, 1331, 1300, 1239, 1200, 1157, 1135, 1073, 1012, 921, 883, 813, 737, 717, 693, 674, 648, 623.

(1-(4-bromophenyl)-2,2,2-trifluoroethyl)triisopropylsilane 2cc



The title compound was prepared following general procedure G on a 0.1 mmol scale from triisopropylsilane and diazo compound 1c. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (26 mg, 66 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2, 2H), 7.20-7.14 (d, *J* = 8.2, 2H), 3.19 (q, $^{3}J_{HF}$ = 13.2, 1H), 1.25-1.13 (m, 3H), 1.08 (d, $^{3}J_{HH}$ = 7.4, 9H), 0.99 (d, $^{3}J_{HH}$ = 7.5, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.7 (q, *J* = 3.5), 132.1, 131.8, 128.2 (q, $^{1}J_{CF}$ = 277.5), 121.0, 39.3 (q, $^{2}J_{CF}$ = 28.6), 18.7, 11.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -56.4 ($^{3}J_{FH}$, *J* = 13.1). HRMS (EI) calculated for $C_8H_5BrF_2^+$ ([M-(iPr)$_3$SiF]$^+$): 217.9543, observed: 217.9557. IR (neat) υ/ cm^{-1} 2958, 2914, 2880, 1491, 1460, 1411, 1338, 1302, 1247, 1200, 1155, 1133, 1074, 1011, 884, 858, 815, 720, 664.

triphenylphosphine (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)borane 5ba



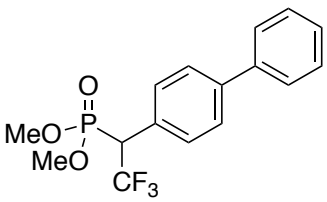
The title compound was prepared following general procedure G on a 0.3 mmol scale from triphenylphosphine borane complex and diazo compound 1b. Purified by silica gel column chromatography (pentane/CH_2Cl_2 9/1 to pentane/CH_2Cl_2 1/1) and obtained as an off-white solid (142 mg, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.52 (d, *J* = 7.7, 2H), 7.48-7.39 (m, 11H), 7.39-7.32 (m, 7H), 7.29 (d, *J* = 8.1, 2H), 7.16 (d, *J* = 8.0, 2H), 2.88-2.72 (m, 1H), 2.80-1.80 (br m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 141.5, 140.7 (m), 138.6, 133.5, 133.4, 131.4 (d, *J* = 2.4), 130.1, 128.9 (d, *J* = 10.2), 128.8, 127.6 (d, *J* = 57.5), 127.1, 127.0, 126.8, 39.7 (m). ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -62.9 (d, $^{3}J_{FH}$ = 11.9). ^{11}B NMR (160 MHz, $CDCl_3$) *δ* -25.6 (m, 1B). ^{31}P NMR (202 MHz, $CDCl_3$) *δ* 16.4 (m). IR (neat) υ/ cm^{-1} 3058, 3012, 2878, 2394, 1484, 1437, 1250, 1119, 1088, 1016, 827, 766, 738, 692. mp 107-108 °C. Compound

5ba was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

Asymmetric reaction was performed using general procedure **H**, diazo **1b** and ligand L8**.** The product (-)-**5ba** was obtained in 83 % yield with this procedure. 72 % *ee* [HPLC conditions; Chiralpak IA column, hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 6.28 min for major isomer, t_R = 6.86 min for minor isomer: $[\alpha]_D^{25}$ = -79.94 (*c* 1.60, $CHCl_3$).

Modified general procedure **H**, using diazo **1b** and ligand **L7**. The product (+)-**5ba** was obtained in 65 % yield and 81 % *ee.* $[\alpha]_D^{25}$ = +89.44 (*c* 0.70, $CHCl_3$).

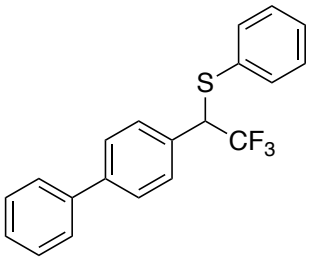
dimethyl (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)phosphonate 3ba



The title compound was prepared following general procedure G on a 0.3 mmol scale from dimethylphosphite and diazo compound 1b. Purified by silica gel column chromatography (99/1 CH_2Cl_2/MeOH to 9/1 CH_2Cl_2/MeOH) and obtained as a white solid (87 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.61 (m, 4H), 7.57 (d, *J* = 7.2, 2H), 7.47 (dd apparent t, *J* = 7.5, 2H), 7.39 (t, *J* = 7.3, 1H), 3.95 (dq, $^2J_{HP}$ = 23.9 and $^3J_{HF}$ = 9.8, 1H), 3.84 (d, $^3J_{PH}$ = 11.2, 3H), 3.63 (d, $^3J_{PH}$ = 11.0, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9 (d, *J* = 2.5), 140.2, 130.8 (d, *J* = 6.2), 129.0, 127.9, 127.7 (d, *J* = 1.7), 127.2, 127.1 (dq, *J* = 7.5, *J* = 1.6), 124.3 (q, $^1J_{CF}$ = 279.5), 54.2 (d, *J* = 6.7), 53.8 (d, *J* = 7.1), 49.8 (dq, $^1J_{CP}$ = 140.0, $^2J_{CF}$ = 29.0). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.6 (t, $^3J_{FH}$ = 9.5). ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.61 (q, *J* = 9.2). HRMS (FI) calculated for $C_{16}H_{16}F_3O_3P$ (M): 344.0789, observed: 344.0798.

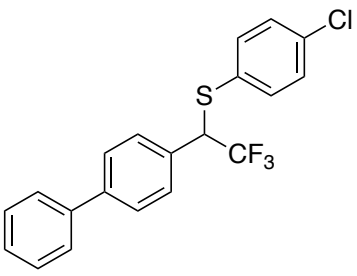
IR (neat) υ/ cm^{-1} 3062, 3032, 2963, 2921, 2859, 1489, 1354, 1254, 1150, 1100, 1042, 837, 758, 726, 693. mp 119-121 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(phenyl)sulfane 4ba



The title compound was prepared following general procedure G on a 0.3 mmol scale from thiophenol and diazo compound 1b. Purified by silica gel column chromatography (99.5/0.5 pentane/ether) and obtained as a white solid (50 mg, 48 %). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.71-7.59 (m, 4H), 7.54-7.44 (m, 6H), 7.41-7.27 (m, 4H), 4.67 (q, $^{3}J_{HF}$ = 8.6, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.31, 140.67, 134.18, 133.18, 133.04, 129.88, 129.78, 129.42, 129.30, 128.27, 127.94, 127.61, 126.29 (q, $^{1}J_{CF}$ = 279.8), 56.87 (q, $^{2}J_{CF}$ = 29.4). ^{19}F NMR (377 MHz, CD_2Cl_2) δ -68.0 (d, $^{3}J_{FH}$ = 8.0). HRMS (CI) calculated for $C_{20}H_{19}F_3NS^+$ ($[M+NH_4]^+$): 362.1190, observed: 362.1188. IR (neat) υ/ cm^{-1} 3076, 2360, 1254, 1146, 1102, 760, 690. mp. 91-93 °C.

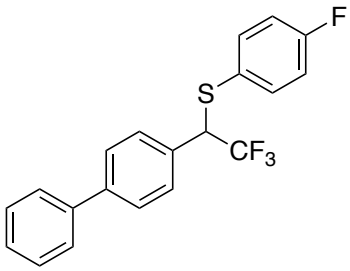
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(4-chlorophenyl)sulfane 4bd



The title compound was prepared following general procedure G on a 0.3 mmol scale from 4-chlorothiophenol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 98/2 pentane/ether) and obtained as a white solid (70 mg, 61 %). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.52-7.50 (m,

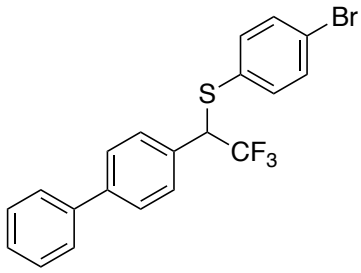
4H), 7.37-7.27 (m, 7H), 7.20-7.18 (m, 2H), 4.51 (q, $^{3}J_{HF}$ = 8.5, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.0, 140.1, 135.4, 135.2, 132.1, 131.0, 129.5, 129.4, 129.0, 127.9, 127.5, 127.1, 125.7 (q, $^{1}J_{CF}$ = 279.8), 56.4 (q, $^{2}J_{CF}$ = 29.5). ^{19}F NMR (377 MHz, $CDCl_3$) δ -67.7 (d, $^{3}J_{FH}$ = 8.5). HRMS (CI) calculated for $C_{20}H_{15}ClF_3S^+$ ($M+H^+$): 379.0535, observed: 379.0536. IR (neat) υ/ cm^{-1} 3726, 3061, 2360, 1251, 1148, 1107, 824, 759. mp 95-96 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(4-fluorophenyl)sulfane 4bc



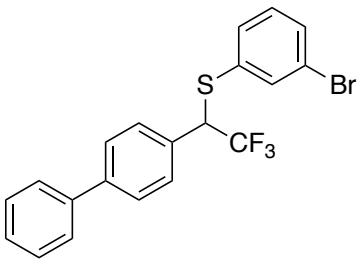
The title compound was prepared following general procedure G on a 0.3 mmol scale from 4-fluorothiophenol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 98/2 pentane/ether) and obtained as a white solid (70 mg, 64 %). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.53-7.50 (m, 4H), 7.39-7.35 (m, 4H), 7.32-7.27 (m, 3H), 6.94-6.91 (m, 2H) 4.49 (q, $^{3}J_{HF}$ = 8.5, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 163.9 (d, $^{1}J_{CF}$ = 249.1), 142.3, 140.6, 137.40 (d, *J* = 8.6), 132.7, 129.9, 129.4, 128.3, 128.0 (d, *J* = 3.4), 127.9, 127.6, 126.2 (q, $^{1}J_{CF}$ = 279.7), 116.8 (d, *J* = 22.0), 57.3 (q, $^{2}J_{CF}$ = 29.4). ^{19}F NMR (377 MHz, CD_2Cl_2) δ -67.78 (d, $^{3}J_{FH}$ = 8), -112.30 (m). HRMS (CI) calculated for $C_{20}H_{14}F_4S^+$ (M^+): 362.0752, observed: 362.0760. IR (neat) υ/ cm^{-1} 3059, 3033, 1488, 1153, 1104, 831, 762, 696. mp 79-81 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(4-bromophenyl)sulfane 4bc



The title compound was prepared following general procedure G on a 0.3 mmol scale from 4-bromothiophenol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 99/1 pentane/ether) and obtained as a white solid (80 mg, 63 %.) ^{1}H NMR (500 MHz, CD_3CN) δ 7.70-7.66 (m, 4H), 7.54-7.44 (m, 6H), 7.43-7.40 (m, 3H), 5.07 (q, $^{3}J_{HF}$ = 8.6, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 142.6, 140.8, 135.9, 133.2, 133.2, 132.6, 130.4, 130.0, 128.9, 128.3, 127.9, 124.6 (q, $^{1}J_{CF}$ = 279.4), 123.4, 55.4 (q, $^{2}J_{CF}$ = 29.3). ^{19}F NMR (377 MHz, CD_3CN) δ -68.33 (d, $^{3}J_{FH}$ = 8.6). HRMS (CI) calculated for $C_{20}H_{14}BrF_3S^+$ (M^+): 421.9952, observed: 421.9950. IR (neat) υ/ cm^{-1} 2980, 2360, 1471, 1253, 1146, 1105, 821. mp 88-90 °C.

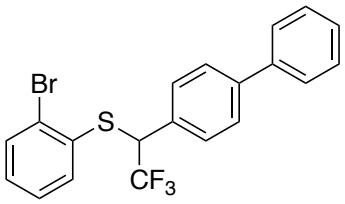
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(3-bromophenyl)sulfane 4bf



The title compound was prepared following general procedure G on a 0.3 mmol scale from 3-bromothiophenol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 99/1 pentane/ether) and obtained as a white solid (86 mg, 68 %). ^{1}H NMR (500 MHz, CD_3CN) δ 7.70-7.66 (m, 5H), 7.55-7.48 (m, 6H), 7.43, 7.43-7.40 (m, 1H), 7.25 (t, *J* = 7.94, 1H), 5.13 (q, $^{3}J_{HF}$ = 8.5, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 142.3, 140.3, 135.7, 135.1, 132.6, 132.2, 132.1, 131.4, 130.0, 129.5, 128.4, 127.9, 127.5, 126.4 (d, $^{1}J_{CF}$ = 279.2), 122.7, 54.7 (q, $^{2}J_{CF}$ = 29.3). ^{19}F NMR (377 MHz, CD_3CN) δ -68.33 (d, $^{3}J_{FH}$ = 8.6). HRMS (CI) calculated for $C_{20}H_{14}BrF_3S^+$ (M^+):

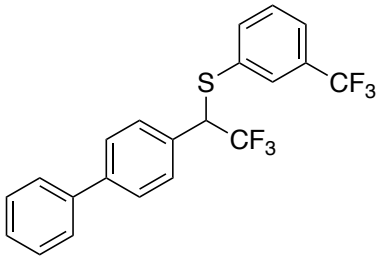
423.9931, observed: 423.9942. IR (neat) υ/ cm^{-1} 3057, 3032, 2360, 2341, 1245, 1150, 1102, 678. mp 58-60 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(2-bromophenyl)sulfane 4bg



The title compound was prepared following general procedure G on a 0.3 mmol scale from 2-bromothiophenol and diazo compound 1b. Purified by silica gel column chromatography (99/1 pentane/Et_2O) and obtained as a white solid (87 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.9, 1.1, 1H), 7.60-7.57 (m, 4H), 7.51 (d, J = 8.1, 2H), 7.45 (t, J = 7.6, 2H), 7.38-7.34 (m, 1H), 7.24 (dd, J = 7.6, 1.1, 2H), 7.18 (td, J = 7.6, 1.4, 1H), 4.80 (q, $^3J_{HF}$ = 8.2, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 140.2, 135.8, 133.6, 133.4, 131.6, 130.3, 129.3, 128.9, 128.8, 128.0, 127.7, 127.5, 127.1, 125.5 (q, $^1J_{CF}$ = 271.5), 54.6 (q, $^2J_{CF}$ = 29.6). ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.4 (d, $^3J_{FH}$ = 8.3, 3F). HRMS (EI) calculated for $C_{20}H_{14}BrF_3S^+$ (M^+): 421.9952, found: 421.9960. IR (neat) υ/ cm^{-1} 3034, 2956, 2921, 2851, 1489, 1446, 1257, 1144, 1099, 861, 757, 684. mp 114-116 °C.

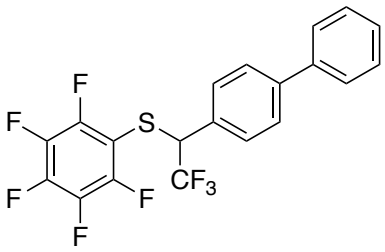
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(3-(trifluoromethyl)phenyl)sulfane 4bi



The title compound was prepared following general procedure G on a 0.3 mmol scale from 3-(trifluoromethyl)thiophenol and diazo compound 1b. Purified by silica gel column chromatography (99/1 pentane/Et_2O) and obtained as a colourless oil (74 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$)

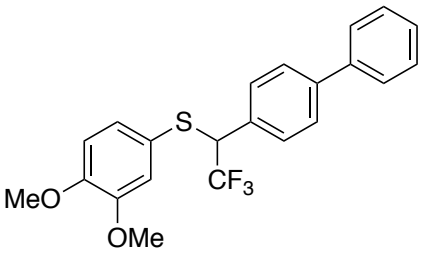
δ 7.70-7.67 (m, 2H), 7.62 (m, 5H), 7.47 (m, 6H), 4.67 (q, $^{3}J_{HF}$ = 8.3, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 140.2, 137.1, 133.7, 131.7, 131.4, 130.6 (q, J = 3.7, 1C), 129.6, 129.3, 128.9, 127.8, 127.6, 127.2, 125.5 (q, J = 3.7), 125.4 (q, $^{1}J_{CF}$ = 274.9), 123.5 (q, $^{1}J_{CF}$ = 272.6), 56.2 (q, $^{2}J_{CF}$ = 29.8). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (s), -67.4 (d, $^{3}J_{FH}$ = 8.4). HRMS (EI) calculated for $C_{21}H_{14}F_6S^+$ (M^+): 412.0745, observed: 412.0743. IR (neat) υ/ cm^{-1} 3061, 3034, 2927, 2855, 2360, 2342, 1488, 1414, 1322, 1250, 1167, 1129, 1105, 1009, 800, 763, 741, 695.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(perfluorophenyl)sulfane 4bh



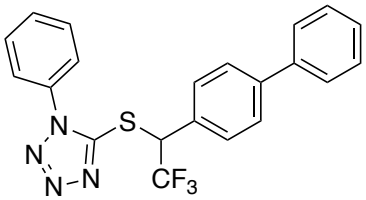
The title compound was prepared following general procedure G on a 0.3 mmol scale from 2,3,4,5,6-pentafluorothiophenol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane) and obtained as a white solid (78 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.47 (m, 4H), 7.38 (t, J = 7.4, 1H), 4.75 (q, $^{3}J_{HF}$ = 7.8, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9-146.8 (m), 142.7, 143.7-141.4 (m), 139.9, 138.9-136.5 (m), 130.0, 129.2, 128.9, 127.9, 127.8, 127.1, 125.0 (q, $^{1}J_{CF}$ = 280.2), 54.1 (q, $^{2}J_{CF}$ = 30.4). ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.2 (d, $^{3}J_{FH}$ = 7.8, 3F), -131.0 (d, $^{3}J_{FF}$ = 18.8, 2F), -149.5 (t, $^{3}J_{FF}$ = 20.8, 1F), -160.0– -160.1 (m, 2F). HRMS (EI) calculated for $C_{20}H_{10}F_8S^+$ (M^+): 434.0375, observed: 434.0362. IR (neat) υ/ cm^{-1} 2923, 2853, 1640, 1518, 1486, 1256, 1142, 1110, 1094, 977, 858, 739, 691. mp. 115-116 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(3,4-dimethoxyphenyl)sulfane 4bb



The title compound was prepared following general procedure G on a 0.3 mmol scale from 3,4-dimethoxythiophenol and diazo compound 1b. Purified by silica gel column chromatography (pentane/Et_2O 3:1) and obtained as a white solid (33 mg, 27 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.5, 5.6, 4H), 7.45 (t, J = 7.6, 2H), 7.39-7.35 (m, 3H), 7.08 (dd, J = 8.4, 1.7, 1H), 6.83 (d, J = 1.6, 1H), 6.78 (d, J = 8.3, 1H), 4.46 (q, $^3J_{HF}$ = 8.7, 1H), 3.87 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 148.8, 141.6, 140.3, 132.7, 129.4, 128.9, 128.6, 127.7, 127.4, 127.1, 125.6 (q, $^1J_{CF}$ = 271.7), 122.7, 118.1, 111.3, 57.2 (q, $^2J_{CF}$ = 29.2), 55.91, 55.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.2 (d, $^3J_{FH}$ = 8.5, 3F). HRMS (EI) Calculated for $C_{22}H_{19}F_3O_2S$ (M^+) 404.1058, Found 404.1067. IR (neat) υ/ cm^{-1} 2998, 2890, 1580, 1503, 1254, 1229, 1143, 1102, 1018, 812, 757, 690. mp 110-111 ^{o}C.

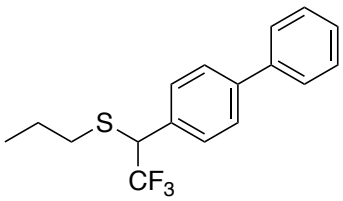
5-((1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)thio)-1-phenyl-1*H*-tetrazole 4bn



The title compound was prepared following general procedure G on a 0.3 mmol scale from 1-phenyl-1*H*-tetrazole-5-thiol and diazo compound 1b. Purified by silica gel column chromatography (9/1 pentane/Et_2O) and obtained as a white solid (106 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.54 (m, 11H), 7.50-7.46 (m, 2H), 7.43-7.38 (m, 1H), 5.95 (q, $^3J_{HF}$ = 8.5, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 142.8, 139.9, 133.1, 130.7, 130.4, 130.0, 129.4, 128.9, 127.9, 127.8, 127.2, 124.6 (q, $^1J_{CF}$ = 272.1), 124.1, 53.4 (q, $^2J_{CF}$ = 31.5). ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.5 (d, $^3J_{FH}$ = 8.3). HRMS (ESI) calculated for

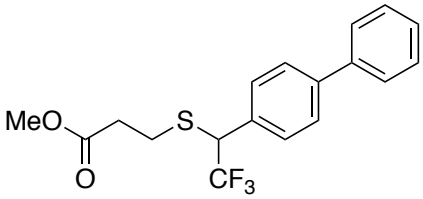
$C_{21}H_{16}F_3N_4S^+$ ($M+H^+$): 413.1042, observed: 413.1039. IR (neat) υ/ cm^{-1} 3071, 3036, 2948, 2922, 1597, 1500, 1410, 1392, 1243, 1167, 1106, 869, 826, 760, 739, 688. mp 80-81 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(propyl)sulfane 4bj



The title compound was prepared following general procedure G on a 0.3 mmol scale from 1-propanethiol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane) and obtained as a colourless oil (72 mg, 77 %). ^{1}H NMR (500 MHz, CD_3CN) δ 7.68-7.64 (m, 4H), 7.52 (d, *J* = 8.4, 2H), 7.49-7.45 (m, 2H), 7.40-7.37 (m, 1H), 4.61 (q, $^3J_{HF}$ = 8.8, 1H), 2.72-2.60 (m, 2H), 1.66-1.55 (m, 2H), 0.94 (t, $^3J_{HH}$ = 7.3, 3H).^{13}C NMR (126 MHz, CD_3CN) δ 142.3, 140.9, 134.4, 130.4, 129.9, 128.8, 128.3, 127.9, 127.4 (q, $^1J_{CF}$ = 278.6), 51.7 (q, $^2J_{CF}$ = 29.4), 35.5, 23.3, 13.4. ^{19}F NMR (377 MHz, CD_3CN) δ -68.79 (d, $^3J_{FH}$ = 9.0, 3F). IR (neat) υ/ cm^{-1} 2956, 2879, 2360, 2341, 1244, 1151, 1131, 1069, 695.

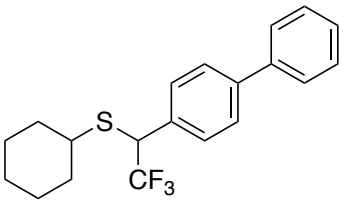
methyl 3-((1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)thio)propanoate 4bm



The title compound was prepared following general procedure G on a 0.3 mmol scale from methyl 3-mercaptopropanoate and diazo compound 1b. Purified by silica gel column chromatography (9/1 pentane/ether to 4/1 pentane/ether) and obtained as a colourless oil (82 mg, 77 %). ^{1}H NMR (400 MHz, aceton-d_6) δ 7.73-7.67 (m, 4H), 7.59 (d, *J* = 8.3, 2H), 7.50-7.45 (m, 2H), 7.40-7.36 (m, 1H), 4.94 (q, $^3J_{HF}$ = 8.8, 1H), 3.63 (d, *J* = 1.7, 3H), 3.03-2.90 (m, 2H), 2.68 (t, $^3J_{HH}$ = 7.0, 2H). ^{13}C NMR (101 MHz, aceton-

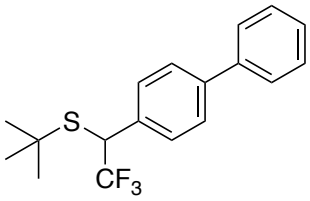
d_6) δ 172.4, 142.3, 140.9, 134.0, 130.4, 129.8, 128.5, 128.1, 127.8, 127.2 (q, $^1J_{CF}$ = 278.5), 51.9, 51.8 (q, $^2J_{CF}$ = 29.5), 34.8, 28.4. ^{19}F NMR (377 MHz, aceton-d_6): δ -68.71 (d, $^3J_{FH}$ = 8.8, 3F). HRMS (CI) calculated for $C_{18}H_{21}F_3NO_2S^+$ ($M+NH_4^+$): 372.1245, observed: 372.1248. IR (neat) υ/ cm^{-1} 3032, 2953, 2360, 2341, 1734, 1248, 1147, 1102.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(cyclohexyl)sulfane 4bl



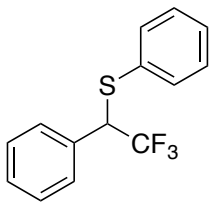
The title compound was prepared following general procedure G on a 0.3 mmol scale from cyclohexanethiol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 97/3 pentane/ether) and obtained as a white solid (100 mg, 95 %). ^{1}H NMR (400 MHz, aceton-d_6) δ 7.71-7.66 (m, 4H), 7.62 (s, 1H), 7.60 (s, 1H), 7.49-7.44 (m, 2H), 7.40-7.35 (m, 1H), 4.85 (q, $^3J_{HF}$ = 9.0, 1H), 2.92-2.86 (m, 1H), 2.00 (s, 1H), 1.76-1.68 (m, 2H), 1.58-1.55 (m, 1H), 1.41-1.22 (m, 6H). ^{13}C NMR (101 MHz, acetone-d_6): δ 142.1, 140.9, 135.0, 130.4, 129.8, 128.5, 127.9, 127.7, 127.2 (q, $^1J_{CF}$ = 278.2), 50.3 (q, $^2J_{CF}$ = 29.2), 45.5, 34.3, 33.9, 26.3. ^{19}F NMR (377 MHz, acetone-d_6) δ -68.70 (d, $^3J_{FH}$ = 8.8, 3F). HRMS (CI) calculated for $C_{20}H_{25}F_3NS^+$ ($M+NH_4^+$): 368.1660, observed: 368.1654. IR (neat) υ/ cm^{-1} 3726, 2930, 2854, 2360, 2340, 1242, 1142, 1091, 820. mp 77-79 °C.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)(tert-butyl)sulfane 4bk



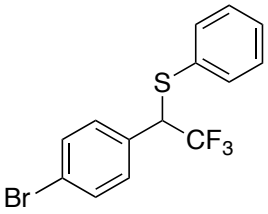
The title compound was prepared following general procedure G on a 0.3 mmol scale from 2-methyl-propane-2-thiol and diazo compound 1b. Purified by silica gel column chromatography (100 % pentane to 97/3 pentane/ether) and obtained as a white solid (81 mg, 83 %). ^{1}H NMR (400 MHz, CD_3CN): δ 7.67-7.63 (m, 4H), 7.55 (d, *J* = 8.2, 2H), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 1H), 4.57 (q, $^{3}J_{HF}$ = 9.4, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, CD_3CN): δ 141.9, 141.0, 136.8, 130.5, 129.92, 128.7, 128.1, 127.9, 127.2 (q, $^{1}J_{CF}$ = 277.4), 49.4 (q, $^{2}J_{CF}$ = 29.3), 46.2, 31.2.^{19}F NMR (377 MHz, CD_3CN): δ -68.56 (d, $^{3}J_{FH}$ = 9.5, 3F). HRMS (CI) calculated for $C_{18}H_{23}F_3NS^+$ ($M+NH_4^+$): 342.1503, observed: 342.1499. IR (neat) υ/ cm^{-1} 3580, 2981, 2889, 2360, 2341, 1151, 1094. mp 97-98 °C.

phenyl(2,2,2-trifluoro-1-phenylethyl)sulfane 4da



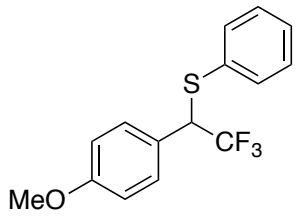
The title compound was prepared following general procedure G on a 0.1 mmol scale from thiophenol and diazo compound 1d. Purified by silica gel column chromatography (100 % pentane to 98/2 pentane/ether) and obtained as a colourless oil (13 mg, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 2H), 7.35 (s, 5H), 7.32-7.25 (m, 3H), 4.52 (q, $^{3}J_{HF}$ = 8.5, 1H). ^{13}C NMR (126MHz, $CDCl_3$) δ 133.9, 133.8, 132.9, 129.3, 129.0, 129.0, 128.9, 128.8, 125.7 (q, $^{1}J_{CF}$ = 279.8), 57.0 (q, $^{2}J_{CF}$ = 29.5). ^{19}F NMR (377 MHz, $CDCl_3$) δ -67.7 (d, $^{3}J_{FH}$ = 8.5). HRMS (CI) calculated for $C_{14}H_{11}F_3S^+$ (M^+): 268.0534, observed: 268.0525. IR (neat) υ/ cm^{-1} 3064, 1249, 1150, 1104, 699. Data consistent with literature values.[205]

phenyl(2,2,2-trifluoro-1-(4-bromo)ethyl)sulfane 4ca



The title compound was prepared following general procedure G on a 0.3 mmol scale from thiophenol and diazo compound 1d. Purified by silica gel column chromatography (100 % pentane) and obtained as a white solid (50 mg, 48 %). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.50 (t, *J* = 2.3, 1H), 7.49 (t, *J* = 2.3, 1H), 7.43-7.41 (m, 2H), 7.34-7.28 (m, 3H), 7.24 (d, *J* = 8.6, 2H), 4.56 (q, $^{3}J_{HF}$ = 8.5, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 134.2, 133.0, 132.4, 132.3, 131.0, 129.6, 129.3, 125.7 (q, $^{1}J_{CF}$ = 279.7), 123.4, 56.4 (q, $^{2}J_{CF}$ = 29.5). ^{19}F NMR (377 MHz, CD_2Cl_2): δ -68.11 (d, $^{3}J_{FH}$ = 8.5, 3F). HRMS (CI) calculated for $C_{14}H_{10}BrF_3S^+$ (M^+): 345.9639, observed: 345.9635. IR (neat) υ/ cm^{-1} 3075, 2359, 1246, 1152, 1104, 1012. mp 40-42 °C. Data consistent with literature values.[207]

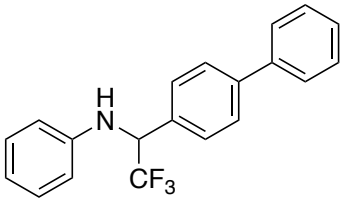
phenyl(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)sulfane 4ea



The title compound was prepared following general procedure G on a 0.3 mmol scale from thiophenol and diazo compound 1e. Purified by silica gel column chromatography (99/1 pentane/ether to 97/3 pentane/ether) and obtained as a white solid (55 mg, 61 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.46-7.42 (m, 2H), 7.32-7.27 (m, 5H), 6.89 (t, *J* = 2.6, 1H), 6.87 (t, *J* = 2.6, 1H), 4.58 (q, $^{3}J_{HF}$ = 8.6, 1H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 160.4, 133.9, 133.1, 130.5, 129.5, 128.9, 126.1 (q, $^{1}J_{CF}$ = 279.5), 125.7, 114.4, 56.2 (q, $^{2}J_{CF}$ = 29.3), 55.6. ^{19}F NMR (377 MHz, CD_2Cl_2) δ -68.39 (d, $^{3}J_{FH}$ = 8.6, 3F). HRMS (CI) calculated for $C_{15}H_{17}F_3NOS^+$ ($M+NH_4^+$): 316.0983, observed: 316.0973. IR (neat) υ/ cm^{-1} 3061, 2936,

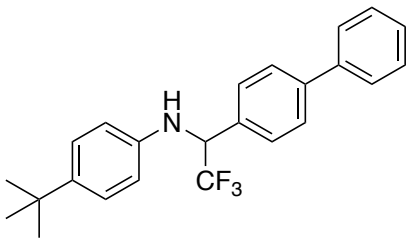
2839, 1513, 1245, 1148, 1100, 822. mp 46-49 °C. Data consistent with literature values.[202]

_N_- (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)aniline 6ba



The title compound was prepared following general procedure G on a 0.3 mmol scale from aniline and diazo compound 1b. Purified by silica gel column chromatography (99/1 pentane/EtOAc to 95/5 pentane/EtOAc) and obtained as a white solid (72 mg, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, J = 7.9, 3H), 7.57 (s, 1H), 7.53 (d, J = 8.2, 2H), 7.44 (t, J = 7.6, 2H), 7.38-7.34 (m, 1H), 7.18 (t, J = 7.8, 2H), 6.79 (t, J = 7.3, 1H), 6.68 (d, J = 8.1, 2H), 4.97 (q, $^{3}J_{HF}$ = 7.3, 1H), 4.36 (br, s, NH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 142.1, 140.3, 133.0, 129.4, 128.8, 128.3, 127.7, 127.1, 125.1 (q, $^{1}J_{CF}$ = 281.9), 119.3, 114.0, 60.3 (q, $^{2}J_{CF}$ = 29.9). ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.93 (d, $^{3}J_{FH}$ = 7.1). HRMS (ESI) calculated for $C_{20}H_{18}NF_3$ ($M+H^+$): 328.1308, observed: 328.1307. IR (neat) υ/ cm^{-1} 3436, 3068, 3029, 1603, 1508, 793, 695. mp 80-81 °C.

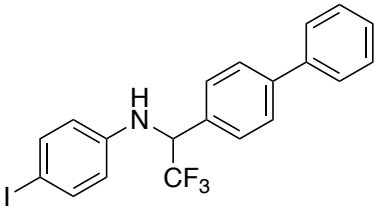
_N_-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)-4-(tert-butyl)aniline 6bb



The title compound was prepared following general procedure G on a 0.3 mmol scale from 4-*tert*-butylaniline and diazo compound 1b. Purified by silica gel column chromatography (99/1 pentane/EtOAc to 95/5 pentane/EtOAc) and obtained as a white solid (94 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.58 (m, 4H), 7.54 (d, J = 8.2, 2H), 7.45 (t, J = 7.6, 2H), 7.36 (t, J = 7.3, 1H),

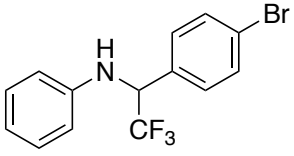
7.21 (d, J = 8.6, 2H), 6.63 (d, J = 8.6, 2H), 4.93 (q, $^{3}J_{HF}$ = 7.3, 1H), 4.28 (br, d, $^{3}J_{HH}$ = 7.0, NH), 1.26 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 142.2, 142.1, 140.5, 133.4, 129.0, 128.5, 127.8, 127.3, 126.3, 125.3 (q, $^{1}J_{CF}$ = 282.0), 113.7, 60.7 (q, $^{2}J_{CF}$ = 29.9), 34.1, 31.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.0 (d, $^{3}J_{FH}$ = 7.5). HRMS (EI) calculated for $C_{24}H_{24}F_3N^+$ (M^+): 383.1855, observed: 383.1871. IR (neat) υ/ cm^{-1} 3425, 3033, 2963, 2867, 1616, 1519, 1485, 1266, 1166, 1100, 817, 766, 728, 696. mp 101-102 °C.

N-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)-4-iodoaniline 6bc



The title compound was prepared following general procedure G on a 0.3 mmol scale from 4-iodoaniline and diazo compound 1b. Purified by silica gel column chromatography (98/2 pentane/ether) and obtained as a yellow solid (85 mg, 62 %). ^{1}H NMR (400 MHz, CD_3CN) δ 7.68-7.58 (m, 6H), 7.47-7.34 (m, 5H), 6.63 (t, J = 2.6, 1H), 6.60 (t, J = 2.6, 1H), 5.58 (br, d, $^{3}J_{HH}$ = 9.7, NH), 5.29-5.21 (m, 1H). ^{13}C NMR (101 MHz, CD_3CN) δ 146.9, 142.6, 140.9, 138.8, 1334.0, 129.9, 129.7, 128.7, 128.3, 127.9, 126.4 (q, $^{1}J_{CF}$ = 281.4), 118.3, 117.1, 59.4 (q, $^{2}J_{CF}$ = 29.8). ^{19}F NMR (377 MHz, CD_3CN) δ -74.27 (d, $^{3}J_{FH}$ = 7.2, 3F). HRMS (CI) calculated for $C_{20}H_{16}F_3IN^+$ ($M+H^+$): 454.0280, observed: 454.0274. IR (neat) υ/ cm^{-1} 3627, 3368, 2360, 2341, 2262, 1488, 1250, 1176, 1127. mp 97-99 °C.

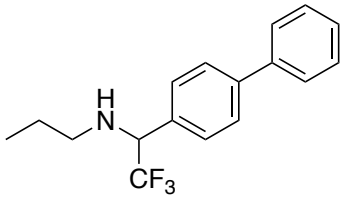
N-(1-(4-bromophenyl)-2,2,2-trifluoroethyl)aniline 6ca



The title compound was prepared following general procedure G on a 0.3 mmol scale from aniline and diazo compound 1c. Purified by silica gel column chromatography (98/2 pentane/ether) and obtained as a viscous colourless oil (75 mg, 76 %). ^{1}H NMR (500 MHz,

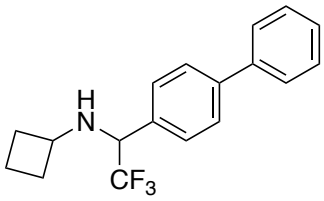
CD_3CN) δ 7.59 (t, *J* = 2.3, 1H), 7.57 (t, *J* = 2.3, 1H), 7.46 (d, *J* = 8.6, 2H), 7.15-7.11 (m, 2H), 6.74-6.70 (m, 3H), 5.35 (br, d, $^3J_{HH}$ = 9.7, NH), 5.26-5.20 (m, 1H).^{13}C NMR (126 MHz, CD_3CN) δ 146.7, 134.8, 132.8, 131.2, 130.2, 126.2 (q, $^1J_{CF}$ = 281.3), 123.6, 119.7, 114.8, 59.4 (q, $^2J_{CF}$ = 29.6). ^{19}F NMR (377 MHz, CD_3CN) δ -74.51 (d, $^3J_{FH}$ = 7.2, 3F). HRMS (CI) calculated for $C_{14}H_{12}BrF_3N^+$ ($M+H^+$): 330.0105, observed: 330.0118. IR (neat) υ/ cm^{-1} 3616, 3092, 2262, 1037, 832, 689. Data consistent with literature values.[138]

_N_-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)propan-1-amine 6be



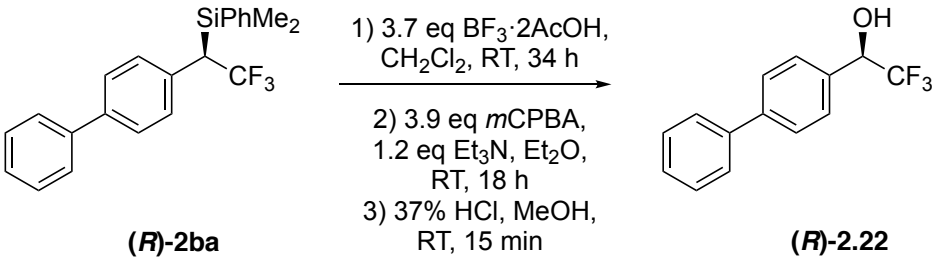
The title compound was prepared following general procedure G on a 0.3 mmol scale from propylamine and diazo compound 1b. Purified by silica gel column chromatography (3/1 pentane/toluene to 1/1 pentane/toluene) and obtained as a white solid (35 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m, 4H), 7.47 (m, 4H), 7.37 (t, *J* = 7.3, 1H), 4.18 (q, $^3J_{HF}$ = 7.4, 1H), 2.63-2.53 (m, 2H), 1.58-1.48 (m, 2H), 1.27 (s, 1H), 0.92 (t, $^3J_{HH}$ = 7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 140.5, 133.6, 128.9, 128.8, 127.6, 127.4, 127.1, 125.6 (q, $^1J_{CF}$ = 281.3), 64.4 (q, $^2J_{CF}$ = 28.1), 49.6, 23.1, 11.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.05 (d, $^3J_{FH}$ = 7.3, 3F). HRMS (ESI) calculated for $C_{17}H_{19}F_3N^+$ ($M+H^+$): 294.1464, observed: 294.1464. IR (neat) υ/ cm^{-1} 2963, 2928, 2856, 1488, 1256, 1152, 1098, 762, 692. mp 53-55 °C.

***N*-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)cyclobutanamine 6bf**



The title compound was prepared following general procedure G on a 0.3 mmol scale from cyclobutylamine and diazo compound 1b. Purified by silica gel column chromatography (1/1 pentane/toluene) and obtained as a waxy solid (84 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.8, 4H), 7.48-7.44 (m, 4H), 7.39-7.35 (m, 1H), 4.14 (q, $^{3}J_{HF}$ = 7.4, 1H), 3.27 (m, 1H), 1.74-1.67 (m, 6H), (N-H peak not observed). ^{13}C NMR (101 MHz, $CDCl_3$) 141.87, 140.45, 133.82, 128.91, 128.81, 127.54, 127.33, 127.12, 125.39 (q, $^{1}J_{CF}$ = 281.4), 62.32 (q, $^{2}J_{CF}$ = 28.8), 52.31, 31.35, 31.27. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.05 (d, $^{3}J_{FH}$ = 7.1, 3F). HRMS (ESI) calculated for $C_{18}H_{19}F_3N^+$(M+H$^+$): 306.1464, observed: 306.14655. IR (neat) υ/ cm^{-1} 3762, 3627, 2924, 2854, 2360, 2341, 1176, 1117.

4.2.7 Determination of Absolute Configuration of Silane



(*R*)-2ba **(*R*)-2.22**

Synthesis of Racemic 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-ol 2.22

To a solution of silane (*rac*)-**2ba** (20.8 mg, 1.0 equiv., 0.0560 mmol) in CH_2Cl_2 (0.6 mL) was added boron trifluoride-acetic acid complex (28 µl, 3.7 equiv., 0.197 mmol). The reaction mixture was stirred for 34 hours at room temperature. The mixture was quenched with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (x2). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, to give the crude fluorosilane (15.8 mg), which was used in subsequent steps without additional purification.

The obtained crude intermediate was dissolved in Et_2O (0.5 mL), and to the resulting solution *m*CPBA (34 mg, 3.9 equiv., 0.197 mmol) following by Et_3N (8.5 µl, 1.2 equiv., 0.061 mmol) was added. The reaction mixture was stirred for 18 h, quenched with sat. aq. $Na_2S_2O_3$, and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The obtained residue was dissolved in MeOH (1 mL) and 2 drops of 37% HCl were added. The reaction mixture was stirred for 15 minutes, the solvent was evaporated, and the residue was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel column chromatography to give the desired product (*rac*)-**2.22** (5.1 mg, 36%) as an off-white solid. ^{1}H NMR (270 MHz, $CDCl_3$): δ, 7.33-7.63 (m, 9H), 5.08 (dq, *J* = 4.60, 6.59, 1H), 2.65 (d, *J* = 4.61, 1H). ^{19}F NMR: δ - 80.4 (d, *J* = 6.60). Data consistent with literature values.[312]

Synthesis of Enantioenriched 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-ol (*R*)-2.22

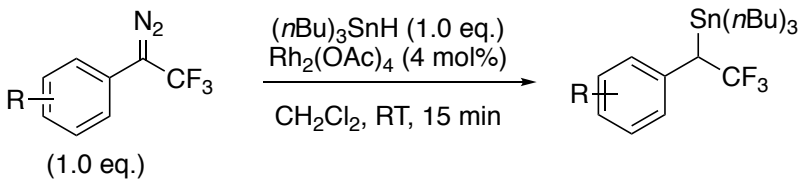
Procedure as per above. Starting from enantioenriched silane (*R*)-**2ba** (19.8 mg, 0.053 mmol) the desired product (*R*)-**2.22** (5.8 mg, 43%) was obtained as an off-white solid.

The Tamao-Fleming oxidation of racemic and enantioenriched silane **2ba** was performed according to modified literature procedure.[311] As this reaction is known to be stereospecific, the absolute configuration of the silane (*R*)-**2ba** was determined by comparison between the measured $[\alpha]_D$ of alcohol (*R*)-**2.22** and previously reported literature values.[312]

Measured for (*R*)-**2.22** $[\alpha]_D^{25}$= –17.7 (*c* 0.39, $CHCl_3$, 96% ee) [lit. (*R*)-**2.22** form $[\alpha]_D^{23}$= –28.5 (*c* 0.99, $CHCl_3$, 96% *ee*); (*S*)-**2.22** form $[\alpha]_D^{23}$= +29.7 (*c* 0.54, $CHCl_3$, >99.9 % *ee*)]. The *ee* was determined by HPLC on Chiralpak IA (hexane/iPrOH = 90/10, 1.0 mL/min, 254 nm), t_R(major) = 8.1 min, t_S(minor) = 9.4 min.

4.2.8 Rhodium-Catalysed Heteroatom-Hydrogen Bond Insertion with $CF_3C(Ar)N_2$

General Procedure I: $CF_3C(Ar)N_2$ Insertion into nBu$_3$SnH under Inert Atmosphere



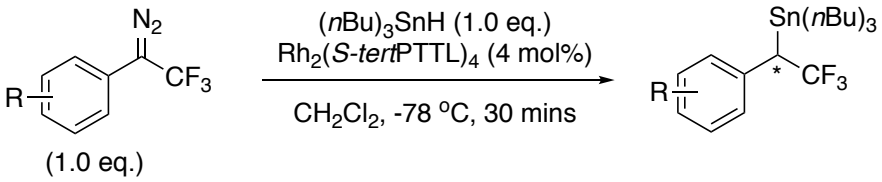
A flame dried, argon purged vial was charged with aryl 2,2,2-trifluorodiazoethane 1b-n (1.0 eq., 0.1 mmol), nBu$_3$SnH (26.5 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added $Rh_2(OAc)_4$ (1.8 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL). Diazo compound 1b-n and nBu$_3$SnH solution was added to the $Rh_2(OAc)_4$ suspension over <1 min at room temperature. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound 1b-n had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 15 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **7** purified by silica gel column chromatography. Note, ^{1}H NMR peaks exhibit characteristic satellite peaks surrounding the signal corresponding to the proton bonded geminal to tin and the trifluoromethyl group – they have been recorded as quartets for clarity. All mass spectrometry results for organotin compounds refer to the ion peak with ^{120}Sn, which in all cases was the most intense peak.

General Procedure J: $CF_3C(Ar)N_2$ Insertion into nBu$_3$SnH in an Open Vial

To a solution of aryl 2,2,2-trifluorodiazoethane 1 (1.0 eq, 0.1 mmol) and nBu$_3$SnH (26.5 µL, 1.0 eq, 0.1 mmol) in CH_2Cl_2 (1.2 mL) in an open vial was added $Rh_2(OAc)_4$ (1.77 mg, 4.0 mol%). After evolution of N_2 had stopped and characteristic orange/red colour of

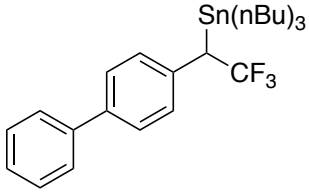
diazo compound 1b-n had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 15 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **7** purified by silica gel column chromatography.

General Procedure K: Asymmetric $CF_3C(Ar)N_2$ Insertion into nBu$_3$SnH



A flame dried, argon purged vial was charged with aryl 2,2,2-trifluorodiazoethane **7b-n** (1.0 eq, 0.1 mmol), nBu$_3$SnH (26.5 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added Rh_2(*S*-*tert*PTTL)$_4$ (1.77 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL) and the mixture was cooled down to -78 °C. The diazo compound **1b-n** and nBu$_3$SnH solution was added to the Rh_2(*S*-*tert*PTTL)$_4$ suspension over <1 min at -78 °C. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound **1b-n** had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 30 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **7** was purified by silica gel column chromatography.

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylstannane 7ba

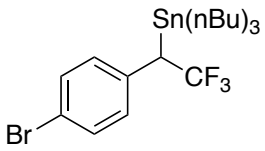


The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1b. Purified by silica gel column chromatography (pentane) and obtained as a

colourless oil (39 mg, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.53 (d, *J* = 8.4, 2H), 7.44 (t, *J* = 7.6, 2H), 7.34 (t, *J* = 7.4, 1H), 7.22 (d, *J* = 8.2, 2H), 3.23 (q, $^{3}J_{HF}$ = 13.7, 1H), 1.47-1.39 (m, 6H), 1.28 (m, 6H), 0.97 (m, 6H), 0.87 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 138.7, 135.8 (q, *J* = 3.8), 129.7 (q, $^{1}J_{CF}$ = 274.3), 128.9, 128.3, 127.5, 127.3, 127.0, 38.9 (q, $^{2}J_{CF}$ = 30.9), 28.8, 27.4, 13.7, 10.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.71 (d, $^{3}J_{FH}$ = 13.6). IR (neat) υ/ cm^{-1}: 3031, 2956, 2923, 2872, 2854, 1907, 1729, 1612, 1600, 1519, 1488, 1463, 1416, 1377, 1345, 1306, 1281, 1261, 1238, 1204, 1123, 1101, 1075, 1039, 1008, 960, 912, 878, 848, 823, 764, 740, 727, 695, 668, 614. HRMS (CI) calculated for $C_{14}H_{10}F_2^{+}$([M-*n*$Bu_3SnF]^{+}$): 216.0751 observed: 216.0753; calculated for $C_{12}H_{27}Sn^{+}$ ([*n*$Bu_3Sn]^{+}$): 291.1129 observed: 291.1145. (Molecular ion could not be detected, but only relevant fragments).

Asymmetric reaction was performed using general procedure K. The product (+)-7ba was obtained in 57 % yield with this procedure. 94 % *ee* [HPLC conditions; Chiralpak IA column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 5.89 min for minor isomer, t_R = 6.72 min for major isomer: $[\alpha]^{D}_{25}$ = +55.7 (*c* 1.46, MeOH).

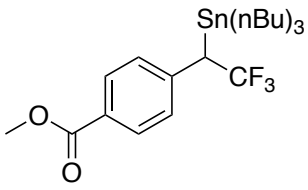
(1-(4-bromophenyl)-2,2,2-trifluoroethyl)tributylstannane 7ca



The title compound was prepared following general procedure J on a 0.1 mmol scale from diazo compound 1c. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (34 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6, 2H), 7.01 (d, *J* = 8.4, 2H), 3.12 (q, $^{3}J_{HF}$ = 13.6, 1H), 1.45-1.37 (m, 6H), 1.29-1.24 (m, 6H), 0.99-0.90 (m, 6H), 0.87 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.9, 131.9, 130.7 (q, $^{1}J_{CF}$ = 275.0), 129.5, 119.6, 38.7 (q,

$^{2}J_{CF}$ = 31.2), 28.7, 27.4, 13.7, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.92 (d, $^{3}J_{FH}$ = 13.5, 3F). IR (neat) υ/ cm^{-1}: 2957, 2924, 2872, 2854, 1895, 1731, 1592, 1490, 1463, 1412, 1377, 1350, 1339, 1301, 1264, 1238, 1196, 1127, 1100, 1076, 1039, 1011, 960, 941, 875, 843, 809, 769, 747, 721, 691, 671, 649. HRMS (CI) calculated for $C_{12}H_{27}Sn^{+}$ ([*n*Bu_3Sn]$^{+}$): 291.1129 observed: 291.1138. (Molecular ion could not be detected).

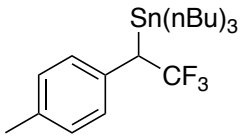
methyl 4-(2,2,2-trifluoro-1-(tributylstannyl)ethyl)benzoate 7ja



The title compound was prepared following general procedure J on a 0.1 mmol scale from diazo compound 1j. Purified by silica gel column chromatography (100% pentane to pentane/CH_2Cl_2 1:1) and obtained as a colourless oil (31 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, $^{3}J_{HH}$ = 8.5, 2H), 7.19 (d, $^{3}J_{HH}$ = 8.3, 2H), 3.90 (s, 3H), 3.25 (q, $^{3}J_{HF}$ = 13.5, 1H), 1.45-1.31 (m, 6H), 1.25 (m, 6H), 1.01-0.89 (m, 6H), 0.85 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.0, 142.5 (q, *J* = 4.0), 130.2, 129.3 (q, $^{1}J_{CF}$ = 275.0), 127.5, 127.4, 52.2, 39.7 (q, $^{2}J_{CF}$ = 31.2), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ -55.31 (d, $^{3}J_{FH}$ = 13.2). IR (neat) υ/ cm^{-1}: 2956, 2925, 2873, 2855, 1724, 1610, 1436, 1348, 1275, 1239, 1184, 1112, 1021, 962, 860, 771, 711. HRMS (CI) calculated for $C_{22}H_{36}F_3O_2Sn^{+}$ ([M+H]$^{+}$): 509.1689 observed: 509.1677.

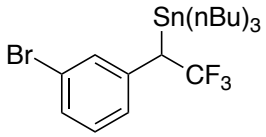
Asymmetric reaction was performed using general procedure **K**. The product (+)-**7ja** was obtained in 77 % yield with this procedure. 84 % *ee* [HPLC conditions; Chiralpak IA column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 10.50 min for major isomer, t_R = 12.13 min for minor isomer: $[\alpha]^{D}_{25}$ = + 1.0 (*c* 1.26, MeOH).

tributyl(2,2,2-trifluoro-1-(*p*-tolyl)ethyl)stannane 7ga



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1g. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (30 mg, 65 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.0, 2H), 7.03 (d, *J* = 8.1, 2H), 3.12 (q, $^{3}J_{HF}$ = 13.8, 1H), 2.31 (s, 3H), 1.47-1.32 (m, 6H), 1.26 (m, 6H), 0.99-0.90 (m, 6H), 0.86 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.4, 133.4 (q, *J* = 3.9), 129.7 (q, $^{1}J_{CF}$ = 275.0), 129.5, 127.9, 38.7 (q, $^{2}J_{CF}$ = 30.8), 28.8, 27.4, 21.1, 13.7, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.04 (d, $^{3}J_{FH}$ = 13.7). IR (neat) υ/ cm^{-1}: 2957, 2923, 2872, 2855, 1513, 1463, 1342, 1309, 1241, 1199, 1123, 1103, 1074, 1042, 876, 808, 719.43, 665. HRMS (CI) calculated for $C_9H_8F_2^+$([M-*n*$Bu_3SnF]^+$): 154.0594 observed: 154.0585; calculated for $C_{12}H_{27}Sn^+$ ([*n*$Bu_3Sn]^+$): 291.1129 observed: 291.1129. (Molecular ion could not be detected, but only relevant fragments).

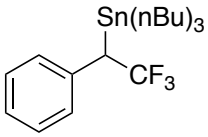
(1-(3-bromophenyl)-2,2,2-trifluoroethyl)tributylstannane 7la



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1l. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (31 mg, 59 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.29 (m, 2H), 7.15 (t, *J* = 8.1, 1H), 7.07 (d, *J* = 7.9, 1H), 3.12 (q, $^{3}J_{HF}$ = 13.5, 1H), 1.45-1.34 (m, 6H), 1.27 (m, 6H), 1.01-0.90 (m, 6H), 0.87 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3-139.1 (m), 130.7, 130.3, 129.3 (q, $^{1}J_{CF}$ = 275.0), 128.9, 126.3, 122.9, 38.9 (q, $^{2}J_{CF}$ = 31.2), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ -55.72 (d, $^{3}J_{FH}$ = 13.4). IR (neat) υ/ cm^{-1}: 2957, 2923, 2872, 2854, 1593, 1563, 1475, 1378, 1341, 1239, 1195, 1128, 1088, 1039, 996, 877, 779, 713, 692, 620.

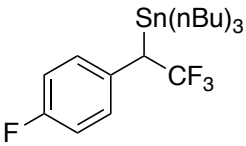
HRMS (CI) calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129 observed: 291.1132. (Molecular ion could not be detected, but only relevant fragments).

tributyl(2,2,2-trifluoro-1-phenylethyl)stannane 7da



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1d. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (22 mg, 49 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 2H), 7.17-7.13 (m, 3H), 3.16 (q, $^3J_{HF}$ = 13.7, 1H), 1.43-1.36 (m, 6H), 1.26 (m, 6H), 0.97-0.90 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.6 (q, *J* = 3.9), 129.7 (q, $^1J_{CF}$ = 274.9), 128.8, 127.9, 125.8, 39.2 (q, $^2J_{CF}$ = 30.9), 28.7, 27.4, 13.7, 10.5. ^{19}F NMR (377 MHz, $CDCl_3$): δ -55.80 (d, $^3J_{FH}$ = 13.5). IR (neat) υ/ cm^{-1}: 2957, 2924, 2872, 2854, 1601, 1495, 1456, 1356, 1277, 1240, 1203, 1125, 1074, 1034, 874, 757, 698, 671, 615. HRMS (CI) calculated for $C_8H_6F_2^+$([M-*n*Bu_3SnF]$^+$): 140.0438 observed: 140.0426; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129 observed: 291.1135. (Molecular ion could not be detected, but only relevant fragments).

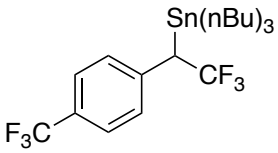
tributyl(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)stannane 7ka



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1k. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (25 mg, 54 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 8.4, 5.4, 2H), 6.98 (t, *J* = 8.7, 2H), 3.13 (q, $^3J_{HF}$ = 13.6, 1H), 1.46-1.34 (m, 6H), 1.26 (m, 6H), 1.00-0.89 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2 (d, $^1J_{CF}$ = 244.5), 132.4 (q, *J* = 3.9), 129.5 (q, $^1J_{CF}$ = 274.9), 129.5 (q, *J* = 7.8), 115.6 (d, *J* = 21.3), 38.3 (q, $^2J_{CF}$ = 31.2), 28.7, 27.4, 13.7,

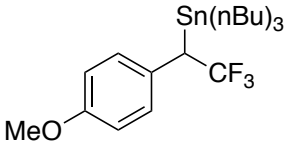
10.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -56.35 (d, $^{3}J_{FH}$ = 3.6, 3F),-117.35– -117.42 (m, 1F). IR (neat) υ/ cm^{-1}: 2958, 2924, 2873, 2855, 1607, 1509, 1464, 1420, 1342, 1272, 1246, 1228, 1200, 1161, 1117, 1094, 1042, 961, 876, 825, 791, 721, 664. HRMS (CI) calculated for $C_8H_5F_3^+$([M-*n*$Bu_3SnF]^+$): 158.0343 observed: 158.0330; calculated for $C_{12}H_{27}Sn^+$ ([*n*$Bu_3Sn]^+$): 291.1129 observed: 291.1133. (Molecular ion could not be detected, but only relevant fragments).

tributyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)stannane 7ia



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1i. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (32 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.1, 2H), 7.24 (d, *J* = 8.2, 2H), 3.24 (q, $^{3}J_{HF}$ = 13.4, 1H), 1.49–1.32 (m, 6H), 1.32–1.16 (m, 6H), 1.02–0.90 (m, 6H), 0.86 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0, 129.1 (q, $^{1}J_{CF}$ = 271.8), 127.8 (q, $^{2}J_{CF}$ = 32.7), 127.6 (t, *J* = 1.4), 125.6 (q, *J* = 3.5), 124.2 (q, $^{1}J_{CF}$ = 271.8), 39.2 (q, $^{2}J_{CF}$ = 31.3), 28.5, 27.2, 13.5, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.51 (d, $^{3}J_{FH}$ = 13.4), -62.44 (m). IR (neat) υ/ cm^{-1}: 2959, 2925, 2874, 2856, 1620, 1582, 1519, 1464, 1423, 1378, 1326, 1286, 1240, 1202, 1166, 1121, 1103, 1069, 1019, 960, 909, 879, 849, 825, 767, 742, 690, 671. HRMS (CI) calculated for $C_{12}H_{27}Sn^+$ ([*n*$Bu_3Sn]^+$): 291.1129 observed: 291.1129. (Molecular ion could not be detected, but only relevant fragments).

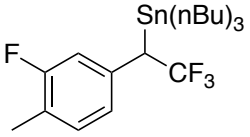
tributyl(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)stannane 7ea



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1e. Purified by preparative TLC (cylcohexane:EtOAc 95:5) and obtained as a colourless oil (18.3 mg, 38 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11–7.02 (m, 2H), 6.87–6.79 (m, 2H), 3.79 (s, 3H), 3.09 (q, $^{3}J_{HF}$ = 13.8, 1H), 1.49-1.30 (m, 6H), 1.26 (h, *J* = 7.3, 6H), 1.02–0.87 (m, 6H), 0.86 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 129.8 (q, $^{1}J_{CF}$ = 274.9), 129.3, 128.5 (q, *J* = 4.2), 114.2, 55.4, 38.1 (q, $^{2}J_{CF}$ = 30.9), 28.8, 27.4, 13.7, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.48 (d, $^{3}J_{FH}$ = 13.6). IR (neat) υ/ cm^{-1}: 2956, 2924, 2872, 2854, 1612, 1581, 1511, 1464, 1443, 1423, 1377, 1351, 1307, 1283, 1250, 1235, 1202, 1180, 1122, 1100, 1075, 1038, 961, 931, 875, 849, 821, 775, 747, 726, 687, 665. HRMS (CI) calculated for $C_9H_8F_2O^+$ ([M-*n*$Bu_3SnF]^+$): 170.0543 observed: 170.0520; calculated for $C_{12}H_{27}Sn^+$ ([*n*$Bu_3Sn]^+$): 291.1129 observed: 291.1116. (Molecular ion could not be detected, but only relevant fragments).

Asymmetric reaction was performed using general procedure K. The product (-)-7ea was obtained in 57 % yield with this procedure. 85 % *ee* [HPLC conditions; Chiralpak IC column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 9.20 min for major isomer, t_R = 10.11 min for minor isomer: $[\alpha]^{D}_{25}$ = -0.6 (*c* 0.46, MeOH).

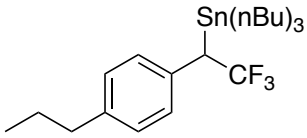
tributyl(2,2,2-trifluoro-1-(3-fluoro-4-methylphenyl)ethyl)stannane 7ma



The title compound was prepared following general procedure I on a 0.05 mmol scale from diazo compound 1m. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (14.5 mg, 60 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13–7.02 (m, 1H), 6.88–6.74 (m, 2H), 3.11 (q, $^{3}J_{HF}$ = 13.6,

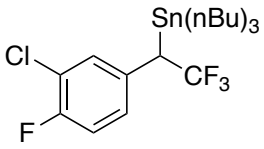
1H), 2.23 (d, *J* = 1.9, 3H), 1.50–1.34 (m, 6H), 1.34–1.13 (m, 6H), 1.04–0.89 (m, 6H), 0.86 (t, $^{3}J_{HH}$ = 7.2, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4 (d, $^{1}J_{CF}$ = 244.6), 136.2 (dd, *J* = 7.8, 3.9), 131.7 (d, *J* = 5.8), 129.5 (q, $^{1}J_{CF}$ = 274.8), 123.3 (d, *J* = 3.1), 122.1 (d, *J* = 17.2), 114.4 (d, *J* = 23.2), 39.2–38.2 (m), 28.7, 27.4, 14.3 (d, *J* = 3.3), 13.7, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.03 (d, $^{3}J_{FH}$ = 13.5, 3F), -117.19 (ddd, *J* = 10.6, 8.4, 2.2, 1F). IR (neat) υ/ cm^{-1}: 2957, 2925, 2873, 2855, 627, 1579, 1510, 1463, 1425, 1378, 1340, 1290, 1272, 1238, 1207, 1150, 1128, 1075, 1041, 999, 958, 876, 851, 817, 787, 755, 710, 683. HRMS (CI) calculated for $C_9H_7F_3^+$ ([M-*n*Bu_3SnF]$^+$): 172.0500 observed: 173.0472; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129 observed: 291.1122. (Molecular ion could not be detected, but only relevant fragments).

tributyl(2,2,2-trifluoro-1-(4-propylphenyl)ethyl)stannane 7ha



The title compound was prepared following general procedure I on a 0.1 mmol scale from diazo compound 1h. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (25 mg, 51 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.2, 2H), 7.04 (d, *J* = 8.2, 2H), 3.13 (q, $^{3}J_{HF}$ = 13.8, 1H), 2.55 (t, *J* = 7.6, 2H), 1.62 (m, 2H), 1.45-1.31 (m, 6H), 1.25 (m, 6H), 0.98-0.89 (m, 9H), 0.85 (t, $^{3}J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.2, 133.6 (q, *J* = 3.9), 129.8 (q, $^{1}J_{CF}$ = 274.8), 128.8, 127.9, 38.7 (q, $^{2}J_{CF}$ = 30.7), 37.7, 28.8, 27.4, 24.6, 13.9, 13.7, 10.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ -56.00 (d, $^{3}J_{FH}$ = 13.8). IR (neat) υ/ cm^{-1}: 2958, 2926, 2872, 2855, 1512, 1463, 1343, 1240, 1198, 1125, 1106, 1041, 877, 668. HRMS (CI) calculated for $C_{11}H_{12}F_2^+$ ([M-*n*Bu_3SnF]$^+$): 182.0907 observed: 182.0905; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129 observed: 291.1136. (Molecular ion could not be detected, but only relevant fragments).

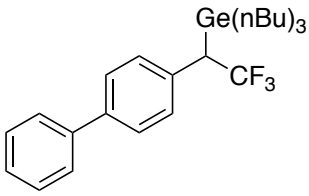
tributyl(1-(3-chloro-4-fluorophenyl)-2,2,2-trifluoroethyl)stannane 7na



The title compound was prepared following general procedure I on a 0.05 mmol scale from diazo compound 1n. Purified by silica gel column chromatography (100% pentane) and obtained as a colourless oil (13 mg, 52 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 6.9, 2.3, 1H), 7.06 (t, *J* = 8.7, 1H), 7.00-6.97 (m, 1H), 3.09 (q, $^{3}J_{HF}$ = 13.4, 1H), 1.44-1.38 (m, 6H), 1.30-1.23 (m, 6H), 0.99-0.92 (m, 6H), 0.87 (t, $^{1}J_{HH}$ = 7.3, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.5 (d, $^{1}J_{CF}$ = 247.8), 134.1-133.8 (m), 129.8, 129.3 (q, $^{1}J_{CF}$ = 275.0), 127.5 (d, *J* = 7.0), 121.2 (d, *J* = 17.9), 116.8 (d, *J* = 21.0), 38.2 (q, $^{2}J_{CF}$ = 31.5), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ -56.22 (d, $^{3}J_{FH}$ = 13.2, 3F), -119.59--119.68 (m, 1F). IR (neat) υ/ cm^{-1}: 2958, 2924, 2855, 1499, 1236, 1230, 1109. HRMS (CI) calculated for $C_8H_4ClF_3^+$ ([M-*n*Bu_3SnF]$^+$): 191.9954 observed: 191.9974; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129 observed: 291.1146. (Molecular ion could not be detected, but only relevant fragments).

4.2.9 Rhodium-Catalysed Germanium-Hydrogen Bond Insertion with $CF_3C(Ar)N_2$

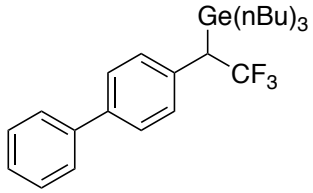
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylgermane 8ba



A flame dried, argon purged vial was charged with diazo compound 1b (26.0 mg, 1.0 eq, 0.1 mmol), *n*Bu_3GeH (25.8 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added $Rh_2(OAc)_4$ (1.77 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL). The diazo compound 1b and *n*Bu_3GeH solution was added to the $Rh_2(OAc)_4$ suspension over <1 min at room temperature. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound 1b had disappeared, the reaction progress was monitored by TLC. After 15 min the reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product 8ba was purified by silica gel column chromatography (pentane) and obtained as a colourless oil in 58% yield (28 mg, 0.06 mmol.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.56-7.53 (m, 2H), 7.47-7.42 (m, 2H), 7.37-7.33 (m, 1H), 7.25 (d, *J* = 7.7, 2H), 3.15 (q, $^3J_{HF}$ = 13.2, 1H), 1.34-1.24 (m, 12H), 0.92-0.83 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.8, 139.3, 134.3, 129.0, 128.9 (q, $^1J_{CF}$ = 276.8), 128.9, 127.4, 127.3, 127.1, 41.0 (q, $^2J_{CF}$ = 28.8), 27.0, 26.6, 13.8, 12.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ -57.08 (d, $^3J_{FH}$ = 13.2). IR (neat) υ/ cm^{-1}: 3032, 2956, 2927, 2871, 2857, 1910, 1600, 1520, 1488, 1464, 1416, 1378, 1344, 1306, 1281, 1262, 1242, 1205, 1141, 1131, 1109, 1063, 1008, 964, 912, 884, 855, 826, 765, 743, 729, 695, 681, 654, 616. HRMS (CI) calculated for $C_{26}H_{41}F_3GeN^+$ ($[M+NH_4]^+$): 498.2397 observed: 498.2435.

4.2.10 Asymmetric Rhodium-Catalysed Germanium-Hydrogen Bond Insertion with $CF_3CH(Ar)N_2$

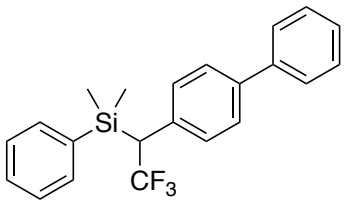
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylgermane 8ba



A flame dried, argon purged vial was charged with diazo compound 1b (1.0 eq, 0.1 mmol), *n*Bu_3GeH (25.8 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added Rh_2(*S-tert*PTTL)$_4$ (1.77 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL) and the mixture was cooled down to -78 °C. The diazo compound 1b and *n*Bu_3GeH solution was added to the Rh_2(*S-tert*PTTL)$_4$ suspension over <1 min at -78 °C. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound **1b** had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 30 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **8ba** was purified by silica gel column chromatography (pentane). The product (+)-8ba was obtained in 99 % yield with this procedure. 99 % *ee* [HPLC conditions; Chiralpak IC column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, t_R = 6.15 min for major isomer, t_R = 6.97 min for minor isomer: $[\alpha]^D_{25}$ = +54.3 (*c* 3.46, MeOH).

4.2.11 Rhodium-Catalysed Silicon-Hydrogen Bond Insertion with $CF_3C(Ar)N_2$

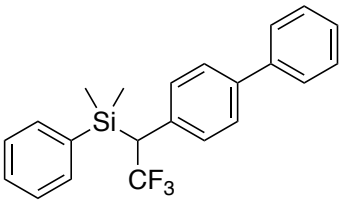
(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane 2ba



A flame dried, argon purged vial was charged with diazo compound **1b** (26.0 mg, 1.0 eq., 0.1 mmol), $PhMe_2SiH$ (15.3 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added $Rh_2(OAc)_4$ (1.77 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL). The diazo compound 1b and $PhMe_2SiH$ solution was added to the $Rh_2(OAc)_4$ suspension over <1 min at room temperature. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound **1b** had disappeared, the reaction progress was monitored by TLC. After 15 minutes the reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **2ba** was purified by silica gel column chromatography (pentane/CH_2Cl_2 95/5 to 85/15) and obtained as a white solid in 92% yield (34 mg, 0.09 mmol). Exhibited identical spectra to the same compound characterised in section 4.2.6.

4.2.13 Asymmetric Rhodium-Catalysed Silicon-Hydrogen Bond Insertion with $CF_3CH(Ar)N_2$

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (*S*)-2ba



A flame dried, argon purged vial was charged with diazo compound 1b (1.0 eq, 0.1 mmol), Me_2PhSiH (15.3 µL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added Rh_2(*S*-*tert*PTTL)$_4$ (1.8 mg, 4.0 mol%) and degassed CH_2Cl_2 (0.5 mL) and the mixture was cooled down to -78 °C. The diazo

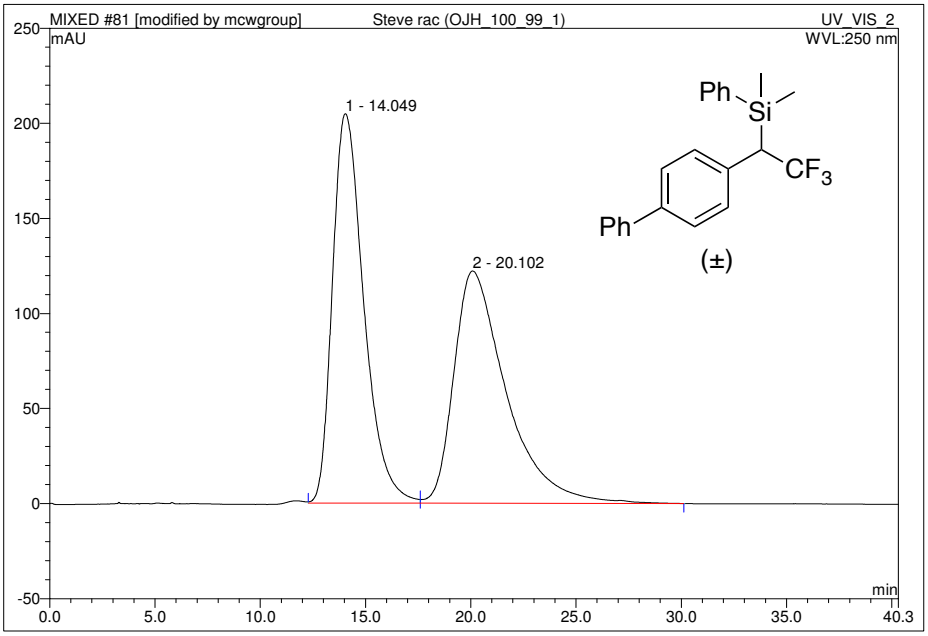
compound 1b and Me_2PhSiH solution was added to the Rh_2(*S*-*tert*PTTL)$_4$ suspension over <1 min at -78 °C. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound **1b** had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 30 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product **(*S*)-2ba** was purified by silica gel column chromatography (pentane/CH_2Cl_2 95/5 to 85/15). Exhibited identical spectra to the same compound characterised in section 4.2.6. The product (+)-2ba was obtained in 65 % and 99 % *ee* [HPLC conditions; Chiralcel OJ-H column, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min, 25 °C, wavelength = 250 nm, t_R = 15.06 min for major isomer, t_R = 20.53 min for minor isomer: $[\alpha]^{D}_{25}$ = + 75.8 (*c* 0.85, MeOH).

4.2.14 HPLC Traces

(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (rac)-2ba

81 Steve rac (OJH_100_99_1)

Sample Name:	**Steve rac (OJH_100_99_1)**	*Injection Volume:*	**8.0**
Vial Number:	**RA8**	*Channel:*	**UV_VIS_2**
Sample Type:	**unknown**	*Wavelength:*	**250**
Control Program:	**A_100_99_1**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**20/11/2015 17:30**	*Sample Weight:*	**1.0000**
Run Time (min):	**40.31**	*Sample Amount:*	**1.0000**

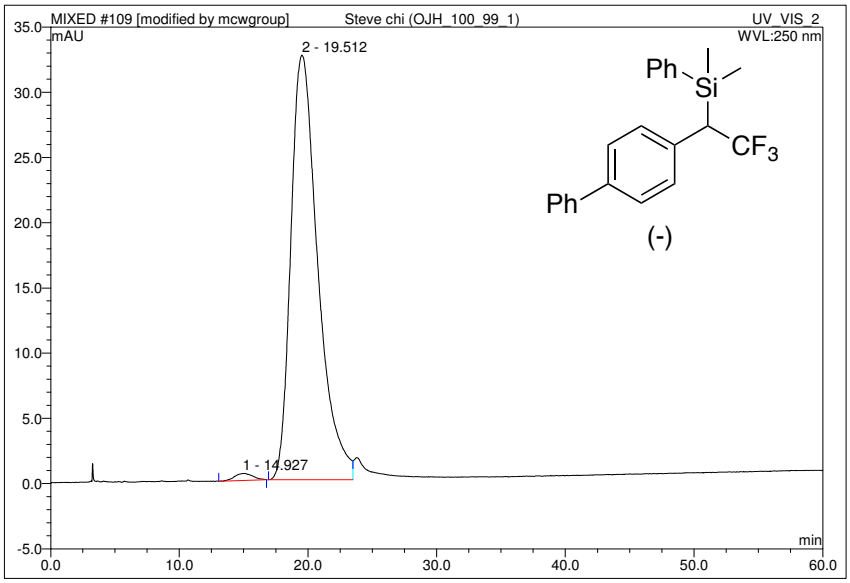


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.05	n.a.	204.850	353.164	50.11	n.a.	M *
2	20.10	n.a.	122.190	351.681	49.89	n.a.	MB*
Total:			327.040	704.845	100.00	0.000	

(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (*R*)-2ba

109 Steve chi (OJH_100_99_1)

Sample Name:	**Steve chi (OJH_100_99_1)**	*Injection Volume:*	**10.0**
Vial Number:	**RA13**	*Channel:*	**UV_VIS_2**
Sample Type:	**unknown**	*Wavelength:*	**250**
Control Program:	**A_100_99_1**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**8/12/2015 12:05**	*Sample Weight:*	**1.0000**
Run Time (min):	**60.00**	*Sample Amount:*	**1.0000**



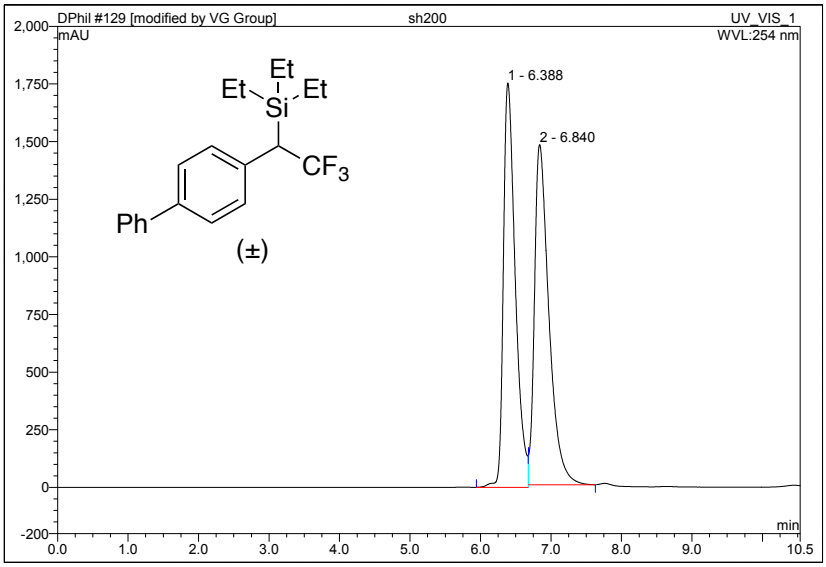
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.93	n.a.	0.540	0.862	1.08	n.a.	BMB*
2	19.51	n.a.	32.548	79.067	98.92	n.a.	BM *
Total:			33.088	79.929	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triethylsilane (rac)-2bb

129 sh200

IA

Sample Name:	**sh200**	*Injection Volume:*	**20.0**
Vial Number:	**266**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**26/11/2015 15:37**	*Sample Weight:*	**1.0000**
Run Time (min):	**10.53**	*Sample Amount:*	**1.0000**



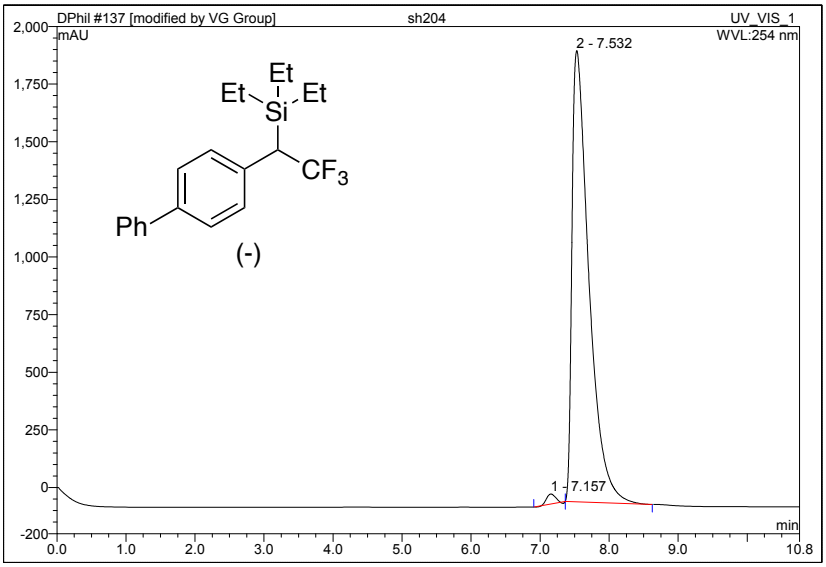
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.39	n.a.	1753.798	343.000	49.50	n.a.	BM *
2	6.84	n.a.	1475.518	349.963	50.50	n.a.	MB*
Total:			3229.316	692.963	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triethylsilane (-)-2bb

137 sh204

IA

Sample Name:	**sh204**	*Injection Volume:*	**20.0**
Vial Number:	**274**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**1/12/2015 16:02**	*Sample Weight:*	**1.0000**
Run Time (min):	**10.76**	*Sample Amount:*	**1.0000**



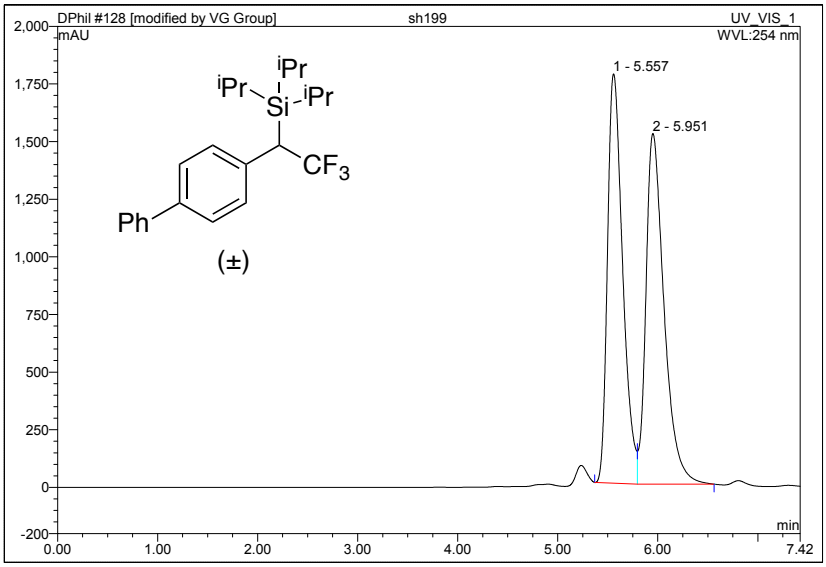
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.16	n.a.	43.518	6.065	1.08	n.a.	BMb*
2	7.53	n.a.	1957.182	556.274	98.92	n.a.	bMB*
Total:			2000.700	562.340	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triisopropylsilane (rac)-2bc

128 sh199

IA

Sample Name:	**sh199**	*Injection Volume:*	**20.0**
Vial Number:	**265**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**26/11/2015 15:24**	*Sample Weight:*	**1.0000**
Run Time (min):	**7.42**	*Sample Amount:*	**1.0000**



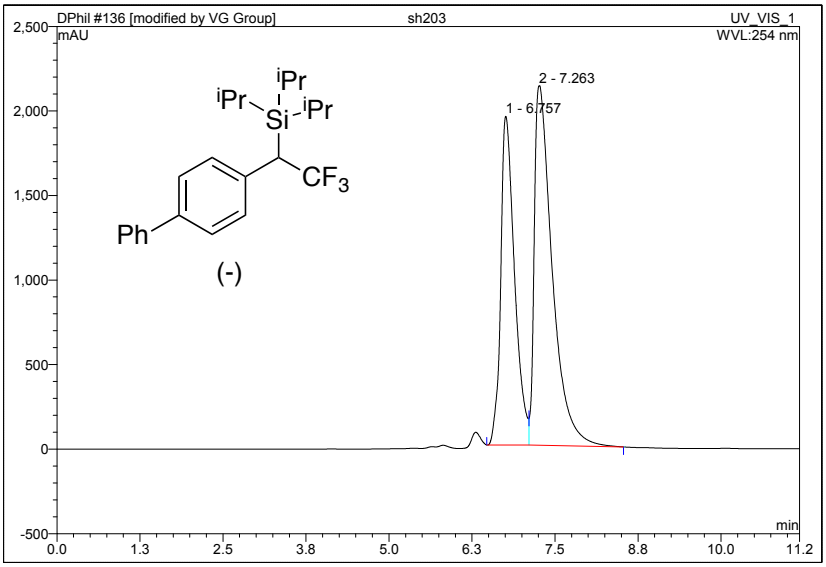
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.56	n.a.	1775.349	311.994	49.39	n.a.	BM *
2	5.95	n.a.	1520.825	319.672	50.61	n.a.	MB*
Total:			3296.174	631.666	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)triisopropylsilane (-)-2bc

136 sh203

IA

Sample Name:	**sh203**	*Injection Volume:*	**20.0**
Vial Number:	**273**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**1/12/2015 15:49**	*Sample Weight:*	**1.0000**
Run Time (min):	**11.18**	*Sample Amount:*	**1.0000**

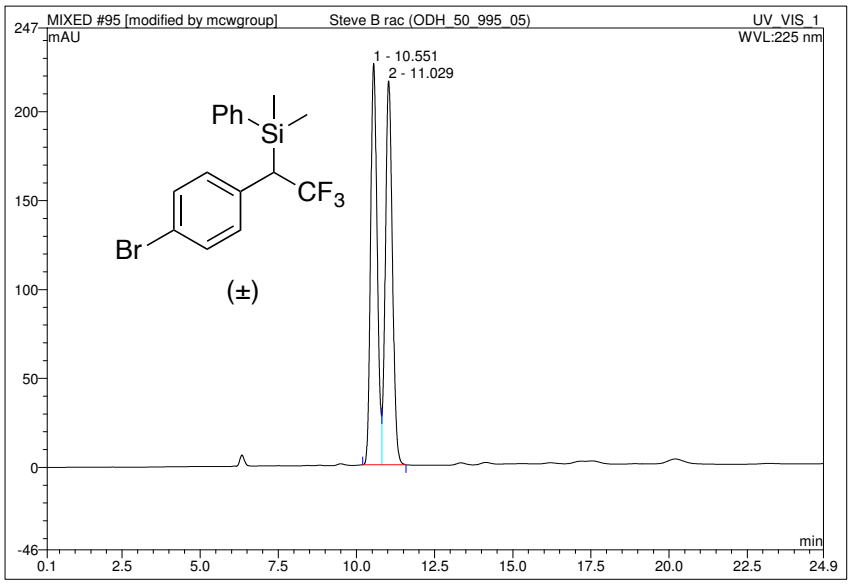


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.76	n.a.	1944.673	469.728	41.32	n.a.	BM *
2	7.26	n.a.	2126.408	667.209	58.68	n.a.	MB*
Total:			4071.081	1136.937	100.00	0.000	

(1-(4-bromophenyl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (rac)-2ca

95 Steve B rac (ODH_50_995_05)

Sample Name:	**Steve B rac (ODH_50_995_05)**	*Injection Volume:*	**8.0**
Vial Number:	**RA9**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**A_50_995_05**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**30/11/2015 17:16**	*Sample Weight:*	**1.0000**
Run Time (min):	**50.00**	*Sample Amount:*	**1.0000**

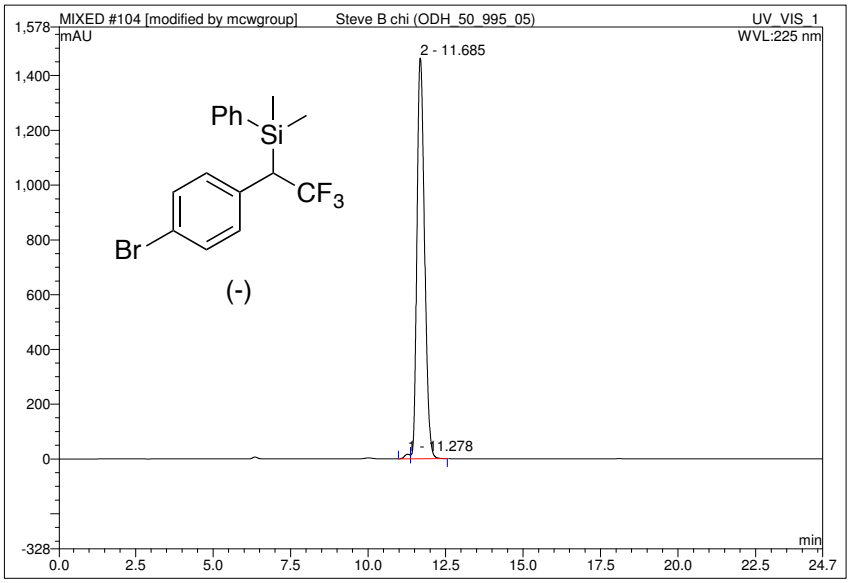


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.55	n.a.	225.554	55.221	49.50	n.a.	BM *
2	11.03	n.a.	215.799	56.339	50.50	n.a.	MB*
Total:			441.353	111.560	100.00	0.000	

(1-(4-bromophenyl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (-)-2ca

104 Steve B chi (ODH_50_995_05)

Sample Name:	**Steve B chi (ODH_50_995_05)**	*Injection Volume:*	**15.0**
Vial Number:	**RA8**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**A_50_995_05**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**4/12/2015 11:46**	*Sample Weight:*	**1.0000**
Run Time (min):	**30.22**	*Sample Amount:*	**1.0000**



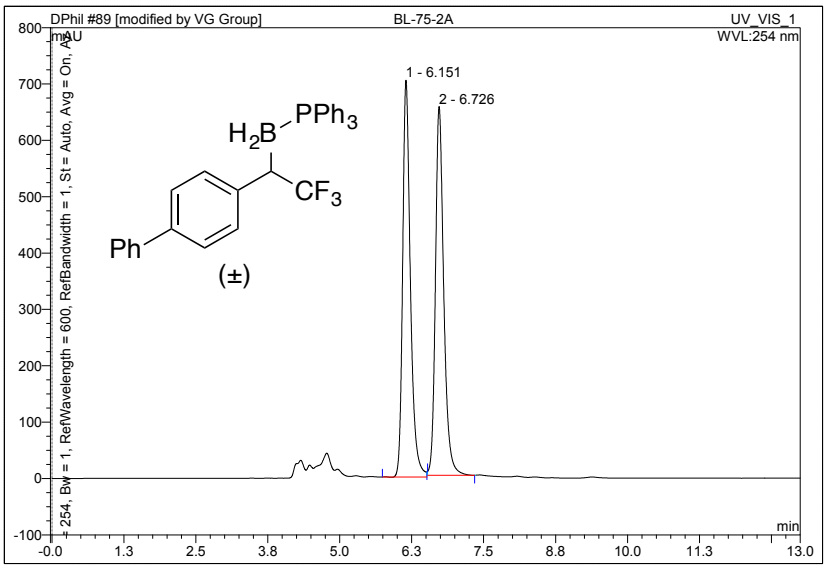
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.28	n.a.	16.860	3.416	0.81	n.a.	BM *
2	11.68	n.a.	1462.925	416.919	99.19	n.a.	MB*
Total:			1479.785	420.335	100.00	0.000	

Triphenylphosphine (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)borane (rac)-5ba

89 BL-75-2A

IA

Sample Name:	**BL-75-2A**	*Injection Volume:*	**20.0**
Vial Number:	**226**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**90 10 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**27/10/2015 22:23**	*Sample Weight:*	**1.0000**
Run Time (min):	**24.82**	*Sample Amount:*	**1.0000**



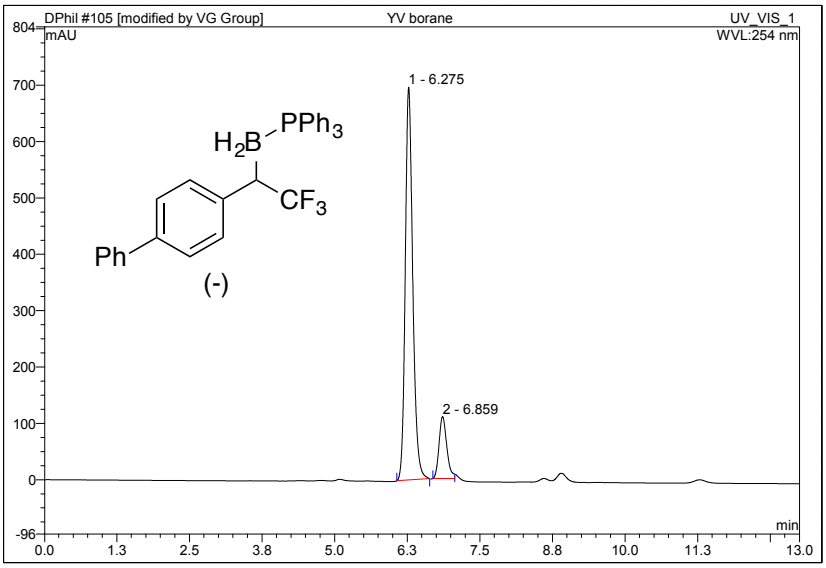
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.15	n.a.	704.071	109.762	50.00	n.a.	BM *
2	6.73	n.a.	654.470	109.768	50.00	n.a.	MB*
Total:			1358.542	219.530	100.00	0.000	

Triphenylphosphine (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)borane (-)-5ba (asymmetric with ligand L8)

105 YV borane

IA

Sample Name:	**YV borane**	*Injection Volume:*	**20.0**
Vial Number:	**242**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**90 10 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**11/11/2015 10:39**	*Sample Weight:*	**1.0000**
Run Time (min):	**18.02**	*Sample Amount:*	**1.0000**



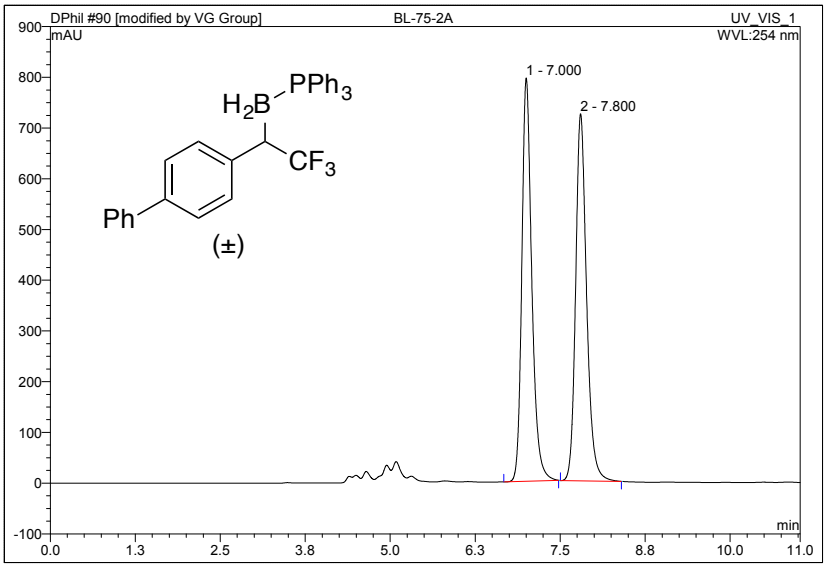
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.28	n.a.	697.048	103.702	85.95	n.a.	BMB*
2	6.86	n.a.	110.045	16.955	14.05	n.a.	BM *
Total:			807.093	120.658	100.00	0.000	

Triphenylphosphine (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)borane (rac)-5ba

90 BL-75-2A

IA

Sample Name:	**BL-75-2A**	*Injection Volume:*	**20.0**
Vial Number:	**227**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**95 5 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**27/10/2015 22:59**	*Sample Weight:*	**1.0000**
Run Time (min):	**11.03**	*Sample Amount:*	**1.0000**



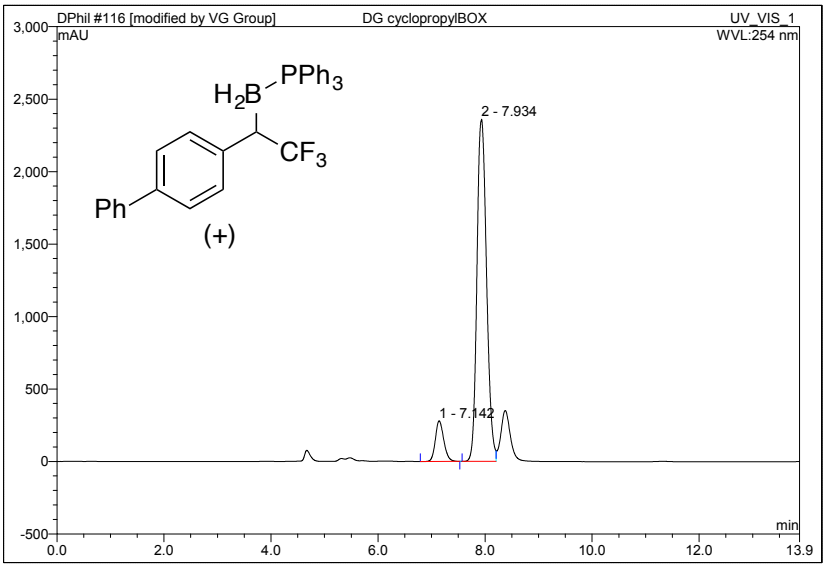
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.00	n.a.	795.011	135.051	50.03	n.a.	BMB*
2	7.80	n.a.	723.700	134.890	49.97	n.a.	BMB*
Total:			1518.711	269.942	100.00	0.000	

Triphenylphosphine (1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)borane (+)-5ba (asymmetric with ligand L7)

116 DG cyclopropylBOX

IA

Sample Name:	**DG cyclopropylBOX**	*Injection Volume:*	**20.0**
Vial Number:	**253**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**95 5 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**16/11/2015 12:18**	*Sample Weight:*	**1.0000**
Run Time (min):	**13.87**	*Sample Amount:*	**1.0000**



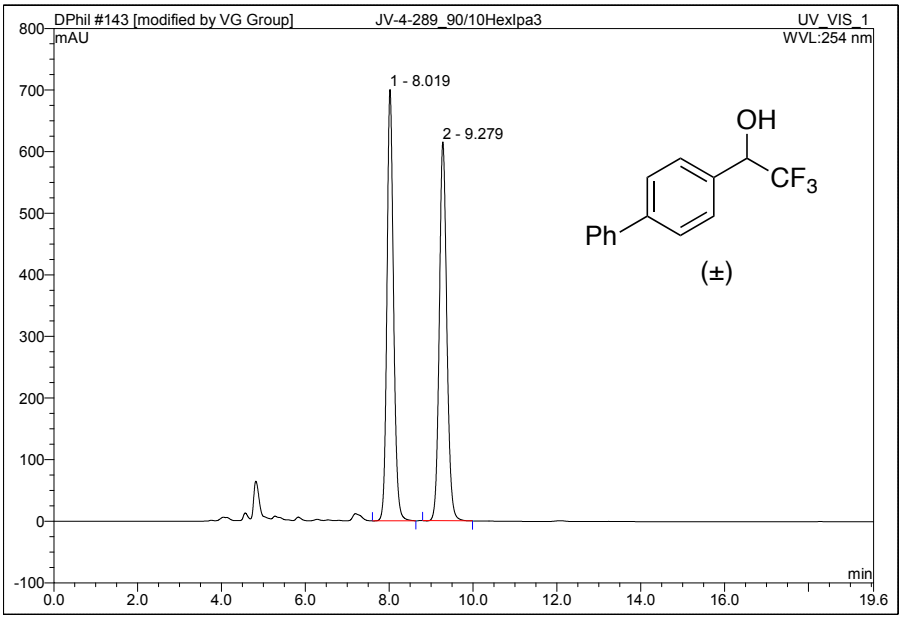
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.14	n.a.	280.643	51.033	9.41	n.a.	BMB*
2	7.93	n.a.	2362.107	491.203	90.59	n.a.	BM *
Total:			2642.750	542.236	100.00	0.000	

1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-ol (rac)-2.22

143 JV-4-289_90/10Hexlpa3

IA

Sample Name:	**JV-4-289_90/10Hexlpa3**	*Injection Volume:*	**20.0**
Vial Number:	**280**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**90 10 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**8/12/2015 11:13**	*Sample Weight:*	**1.0000**
Run Time (min):	**19.55**	*Sample Amount:*	**1.0000**



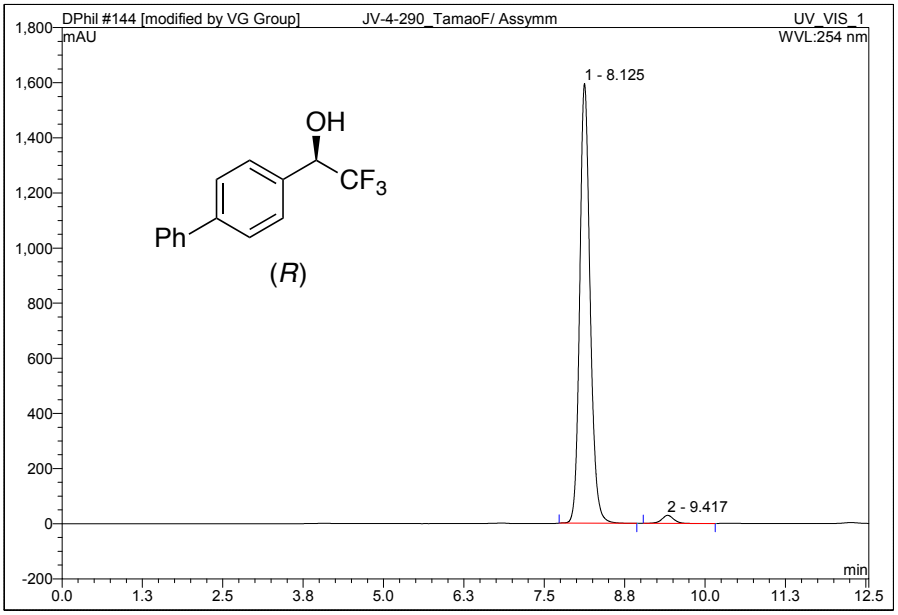
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.02	n.a.	700.298	127.834	50.02	n.a.	BMB*
2	9.28	n.a.	615.168	127.754	49.98	n.a.	BMB*
Total:			1315.466	255.588	100.00	0.000	

1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-ol (*R*)-2.22

144 JV-4-290_TamaoF/ Assymm

IA

Sample Name:	**JV-4-290_TamaoF/ Assymm**	*Injection Volume:*	**20.0**
Vial Number:	**281**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**90 10 CD 1mLmin 40 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**8/12/2015 17:41**	*Sample Weight:*	**1.0000**
Run Time (min):	**12.55**	*Sample Amount:*	**1.0000**

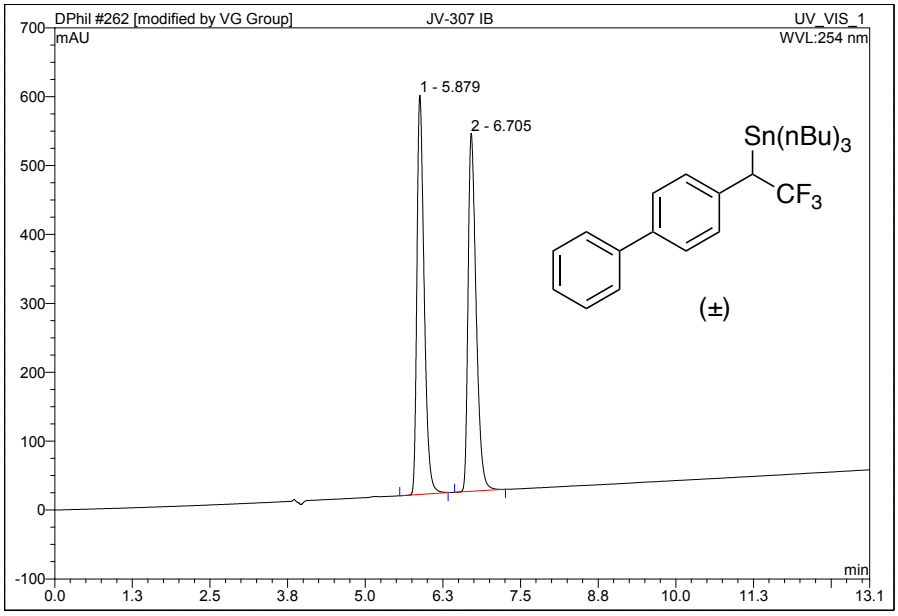


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.12	n.a.	1595.893	298.570	97.94	n.a.	BMB*
2	9.42	n.a.	29.393	6.275	2.06	n.a.	BMB*
Total:			1625.285	304.846	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylstannane (rac)-7ba

262 JV-307 IB

Sample Name:	**JV-307 IB**	*Injection Volume:*	**20.0**
Vial Number:	**397**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 35 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**13/6/2016 10:38**	*Sample Weight:*	**1.0000**
Run Time (min):	**13.12**	*Sample Amount:*	**1.0000**



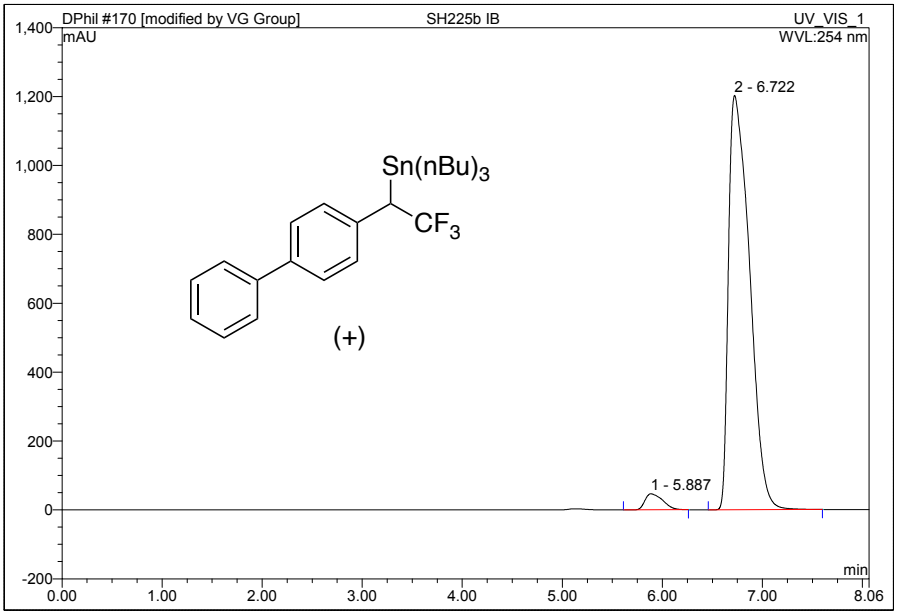
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.88	n.a.	579.408	78.155	49.91	n.a.	BMB*
2	6.71	n.a.	519.379	78.423	50.09	n.a.	BMB*
Total:			1098.787	156.578	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylstannane (+)-7ba

170 SH225b IB

IA

Sample Name:	**SH225b IB**	*Injection Volume:*	**20.0**
Vial Number:	**307**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**22/2/2016 17:52**	*Sample Weight:*	**1.0000**
Run Time (min):	**8.06**	*Sample Amount:*	**1.0000**



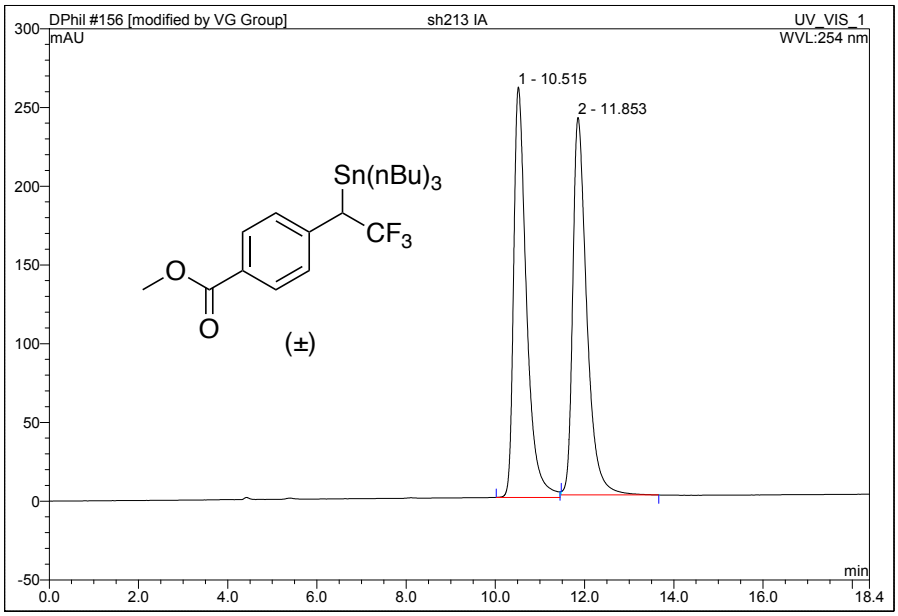
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.89	n.a.	46.499	9.550	3.16	n.a.	BMB*
2	6.72	n.a.	1202.962	292.858	96.84	n.a.	BMB*
Total:			1249.461	302.408	100.00	0.000	

methyl 4-(2,2,2-trifluoro-1-(tributylstannyl)ethyl)benzoate (rac)-7ja

156 sh213 IA

IA

Sample Name:	**sh213 IA**	*Injection Volume:*	**20.0**
Vial Number:	**293**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**Default**	*Dilution Factor:*	**1.0000**
Recording Time:	**14/2/2016 23:32**	*Sample Weight:*	**1.0000**
Run Time (min):	**18.39**	*Sample Amount:*	**1.0000**

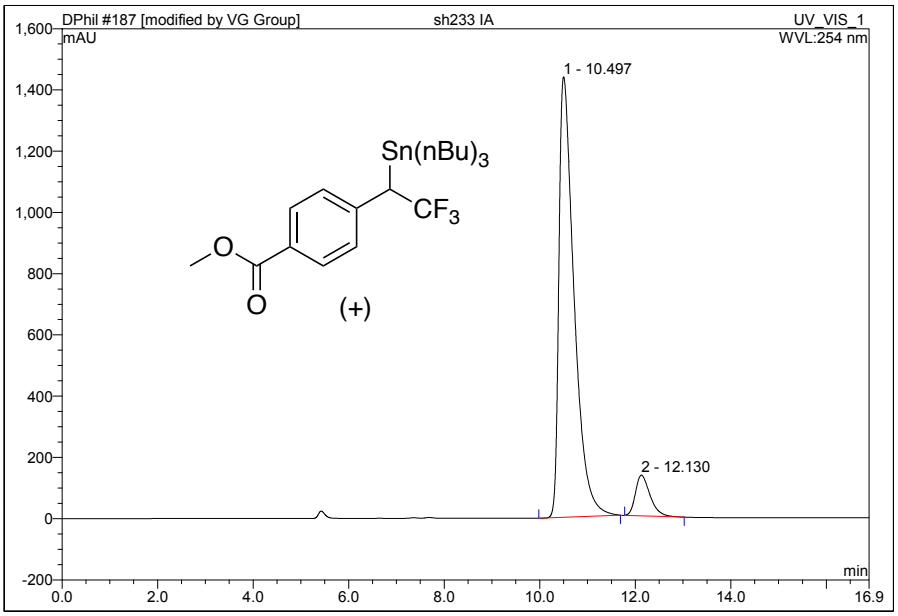


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.52	n.a.	260.585	86.884	49.89	n.a.	BM *
2	11.85	n.a.	239.677	87.272	50.11	n.a.	MB*
Total:			500.261	174.156	100.00	0.000	

methyl 4-(2,2,2-trifluoro-1-(tributylstannyl)ethyl)benzoate (+)-7ja

187 sh233 IA

Sample Name:	**sh233 IA**	*Injection Volume:*	**20.0**
Vial Number:	**322**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**7/3/2016 17:09**	*Sample Weight:*	**1.0000**
Run Time (min):	**16.89**	*Sample Amount:*	**1.0000**

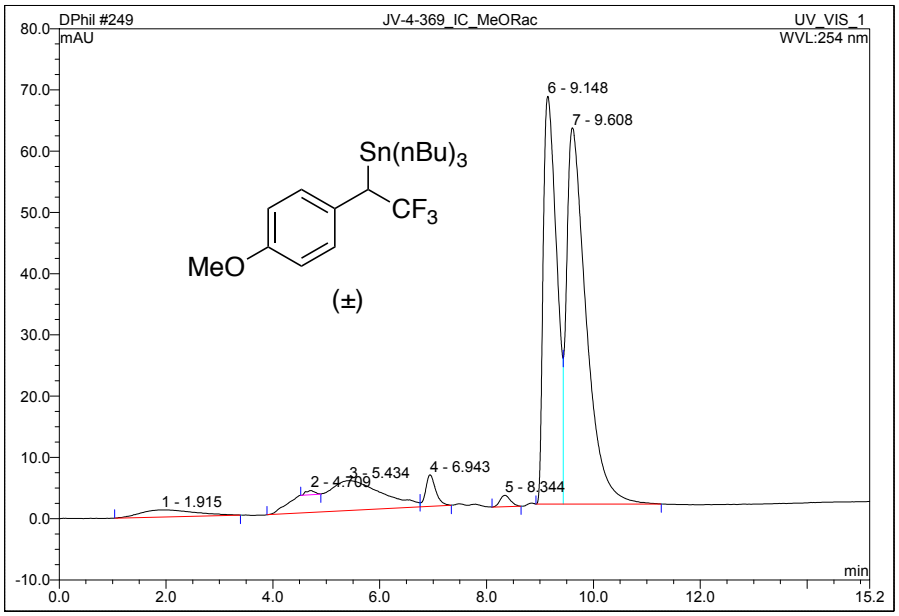


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.50	n.a.	1438.265	528.506	91.84	n.a.	BMB*
2	12.13	n.a.	132.731	46.939	8.16	n.a.	BMB*
Total:			1570.996	575.445	100.00	0.000	

tributyl(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)stannane (rac)-7ea

249 JV-4-369_IC_MeORac

Sample Name:	**JV-4-369_IC_MeORac**	*Injection Volume:*	**20.0**
Vial Number:	**384**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**26/4/2016 10:55**	*Sample Weight:*	**1.0000**
Run Time (min):	**15.17**	*Sample Amount:*	**1.0000**

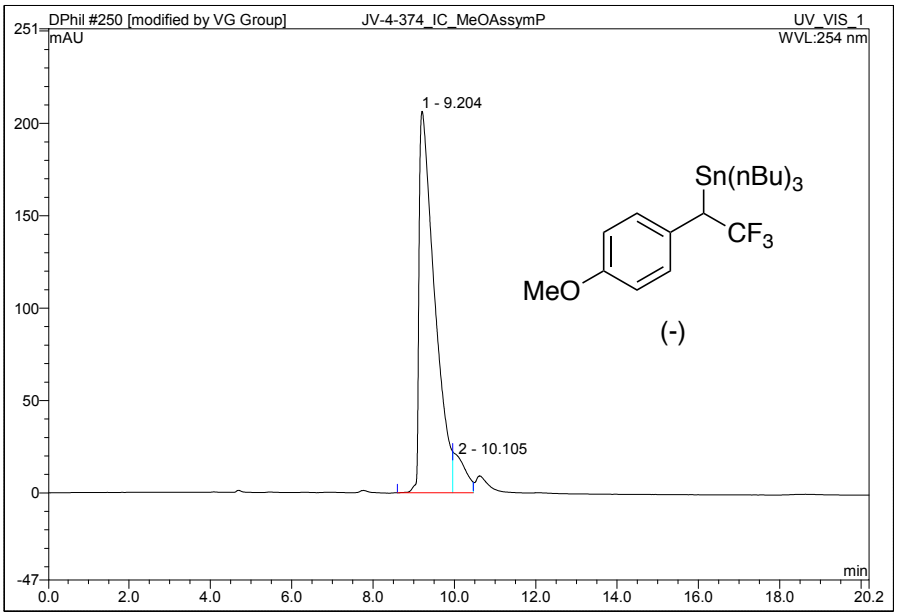


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	1.91	n.a.	1.170	1.375	2.44	n.a.	BMB
2	4.71	n.a.	0.683	0.133	0.24	n.a.	Ru
3	5.43	n.a.	4.885	7.501	13.30	n.a.	BM
4	6.94	n.a.	5.144	1.124	1.99	n.a.	MB
5	8.34	n.a.	1.863	0.423	0.75	n.a.	BMB
6	9.15	n.a.	66.581	19.541	34.64	n.a.	BM
7	9.61	n.a.	61.451	26.312	46.64	n.a.	MB
Total:			141.778	56.410	100.00	0.000	

tributyl(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)stannane (-)-7ea

250 JV-4-374_IC_MeOAssymP

Sample Name:	**JV-4-374_IC_MeOAssymP**	*Injection Volume:*	**20.0**
Vial Number:	**385**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**26/4/2016 13:00**	*Sample Weight:*	**1.0000**
Run Time (min):	**57.77**	*Sample Amount:*	**1.0000**

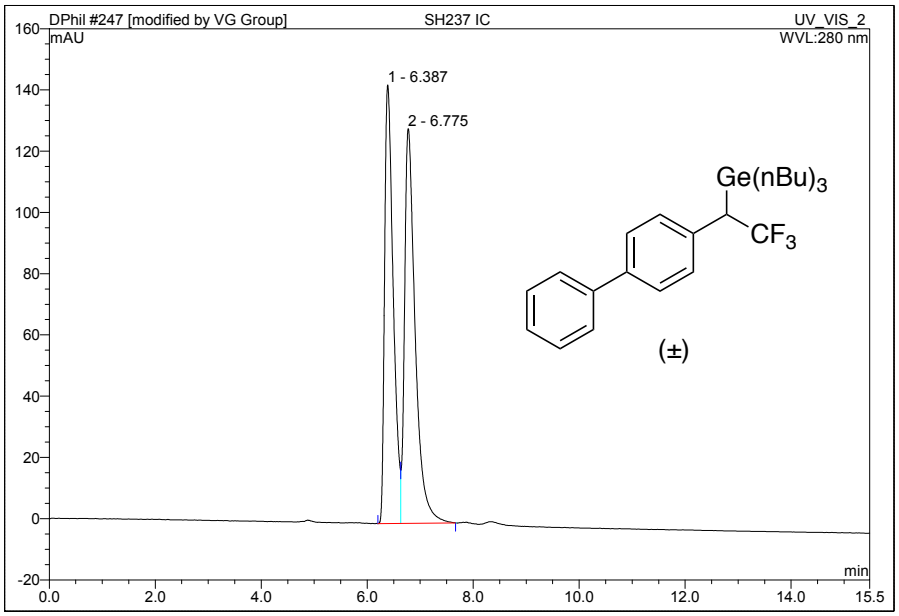


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.20	n.a.	206.448	90.889	92.53	n.a.	BM *
2	10.10	n.a.	19.203	7.343	7.47	n.a.	M *
Total:			225.651	98.231	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylgermane (rac)-8ba

247 SH237 IC

Sample Name:	**SH237 IC**	*Injection Volume:*	**20.0**
Vial Number:	**382**	*Channel:*	**UV_VIS_2**
Sample Type:	**unknown**	*Wavelength:*	**280**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**24/4/2016 17:38**	*Sample Weight:*	**1.0000**
Run Time (min):	**15.48**	*Sample Amount:*	**1.0000**

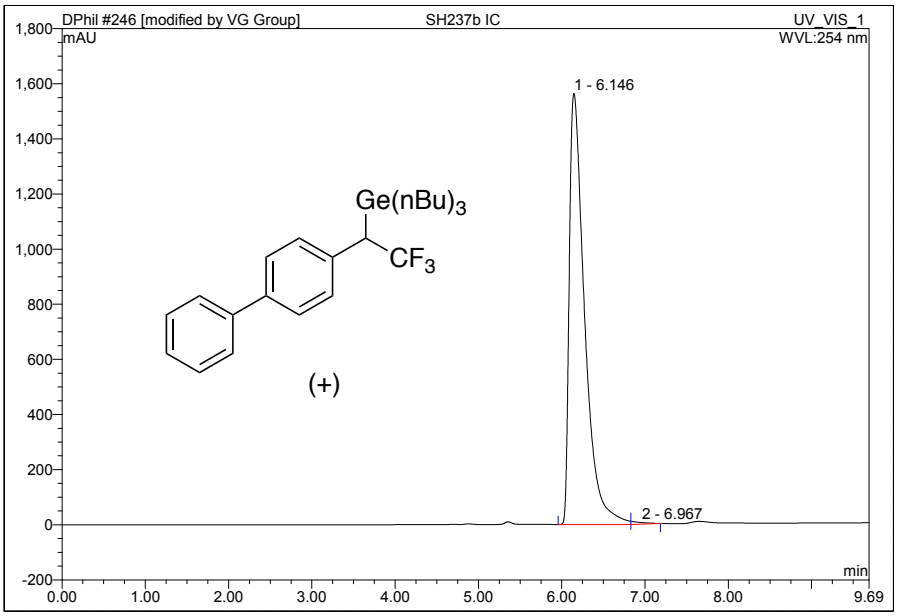


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.39	n.a.	143.264	27.027	47.36	n.a.	BM
2	6.78	n.a.	128.905	30.040	52.64	n.a.	MB
Total:			272.169	57.068	100.00	0.000	

(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)tributylgermane (+)-8ba

246 SH237b IC

Sample Name:	**SH237b IC**	*Injection Volume:*	**20.0**
Vial Number:	**381**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**100 C 1mLmin 60 min**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**24/4/2016 17:21**	*Sample Weight:*	**1.0000**
Run Time (min):	**9.69**	*Sample Amount:*	**1.0000**

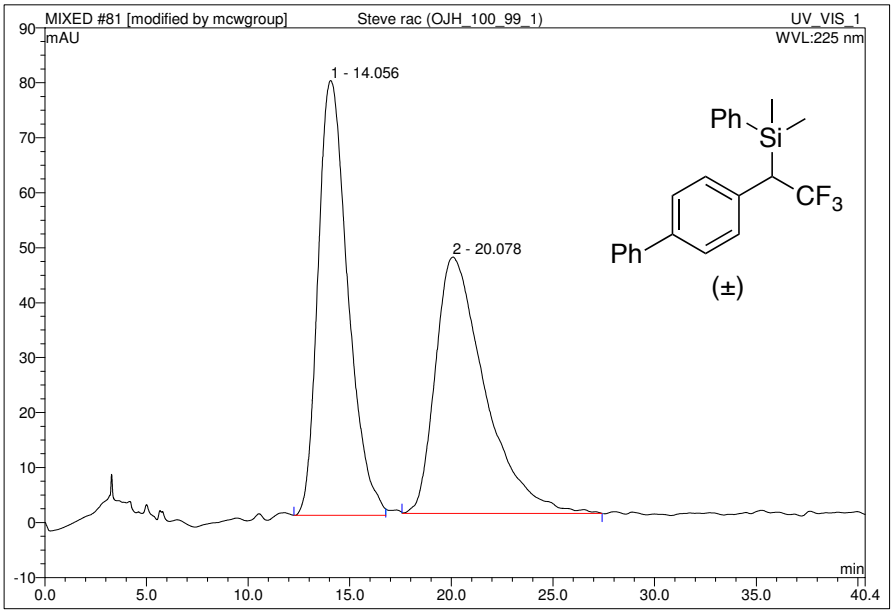


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.15	n.a.	1564.169	332.749	99.52	n.a.	BM *
2	6.97	n.a.	5.254	1.618	0.48	n.a.	MB*
Total:			1569.422	334.368	100.00	0.000	

(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (rac)-2ba

81 Steve rac (OJH_100_99_1)

Sample Name:	**Steve rac (OJH_100_99_1)**	*Injection Volume:*	**8.0**
Vial Number:	**RA8**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**A_100_99_1**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**20/11/2015 17:30**	*Sample Weight:*	**1.0000**
Run Time (min):	**40.36**	*Sample Amount:*	**1.0000**

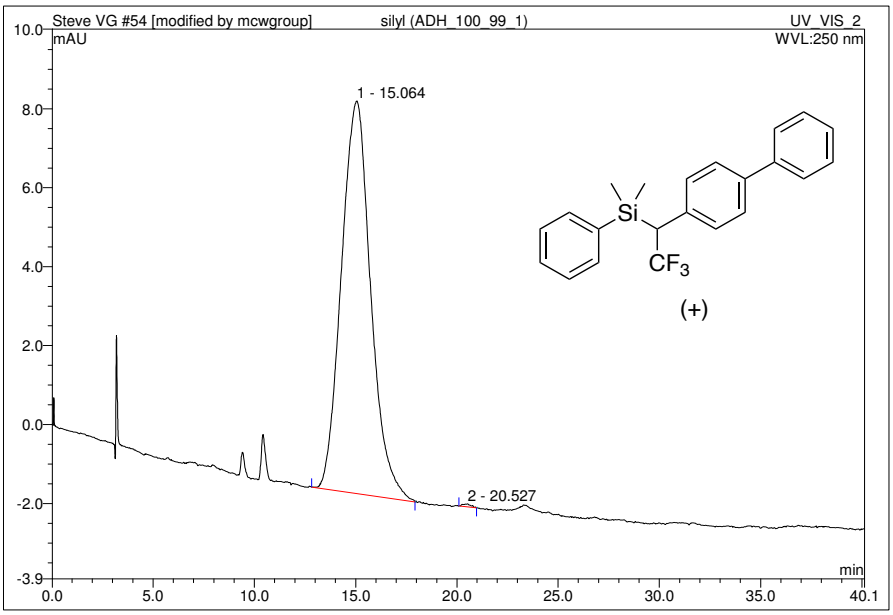


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.06	n.a.	79.092	134.666	50.61	n.a.	BM *
2	20.08	n.a.	46.645	131.424	49.39	n.a.	MB*
Total:			125.736	266.090	100.00	0.000	

(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethyl)dimethyl(phenyl)silane (+)-2ba

54 silyl (ADH_100_99_1)

Sample Name:	**silyl (ADH_100_99_1)**	*Injection Volume:*	**8.0**
Vial Number:	**RA8**	*Channel:*	**UV_VIS_2**
Sample Type:	**unknown**	*Wavelength:*	**250**
Control Program:	**A_100_99_1**	*Bandwidth:*	**1**
Quantif. Method:	**Standard**	*Dilution Factor:*	**1.0000**
Recording Time:	**25/7/2016 17:21**	*Sample Weight:*	**1.0000**
Run Time (min):	**51.85**	*Sample Amount:*	**1.0000**

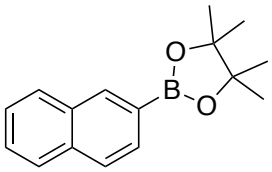


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.06	n.a.	9.946	16.672	99.80	n.a.	BMB*
2	20.53	n.a.	0.079	0.033	0.20	n.a.	BMB*
Total:			10.024	16.706	100.00	0.000	

4.3 Experimental Procedures and Characterisation Data for Chapter 3

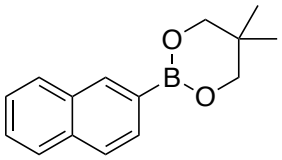
4.3.1 Preparation of Boronic ester species 9

4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane 9b



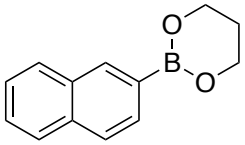
2-naphthylboronic acid (1.38 g, 8.0 mmol) and pinacol (945 mg, 8.0 mmol) were dissolved in anhydrous Et_2O (50 mL) and stirred at room temperature for 1 hour. The mixture was then concentrated *in vacuo* and the crude product purified by silica gel column chromatography (100% pentane to 98/2 pentane/ Et_2O) and obtained as a white solid (2.0 g, 99 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.38 (d, *J* = 0.6, 1H), 7.84 (t, *J* = 1.0, 4H), 7.50 (t, *J* = 1.7, 2H), 1.40 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.4, 135.2, 132.9, 130.5, 128.8, 127.8, 127.1, 125.9, 84.1, 77.2, 25.1, (C-B not observed). Data consistent with literature values.[383]

5,5-dimethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborinane 9c



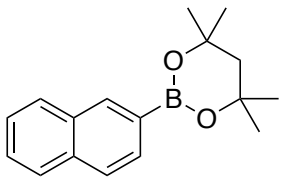
2-naphthylboronic acid (13.8 g, 80.0 mmol) and neopentyl glycol (8.33 g, 80.0 mmol) were dissolved in anhydrous Et_2O (250 mL). $MgSO_4$ (9.6 g, 80 mmol) was added to the solution which was stirred at room temperature for 16 hours. The mixture was filtered through a plug of cotton wool, concentrated *in vacuo*, purified by silica gel column chromatography (9/1 pentane Et_2O) and obtained as a white solid (16.2 g, 85 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.36 (s, 1H), 7.90-7.81 (m, 4H), 7.52-7.44 (m, 2H), 3.84 (s, 4H), 1.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.2, 135.0, 133.0, 130.1, 128.8, 127.8, 126.9, 126.8, 125.7, 72.6, 32.1, 22.1, (C-B not observed). Data consistent with literature values.[384]

2-(naphthalen-2-yl)-1,3,2-dioxaborinane 9d



2-naphthylboronic acid (2.0 g, 11.6 mmol) and 1,3-propanediol (880 mg, 11.6 mmol) were dissolved in anhydrous THF (60 mL). $MgSO_4$ (1.4 g, 11.6 mmol) was added to the solution which was refluxed for 16 hours. The mixture was filtered through a plug of cotton wool, concentrated *in vacuo*, purified by silica gel column chromatography (1/1 pentane Et_2O) and obtained as a white solid (2.2 g, 88 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.34 (s, 1H), 7.91-7.82 (m, 4H), 7.54-7.45 (m, 2H), 4.23 (t, *J* = 5.5, 4H), 2.10 (quintet, *J* = 5.5, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.0, 134.9, 133.0, 129.9, 128.8, 127.8, 126.9, 126.7, 125.7, 62.2, 27.6, (C-B not observed). Data consistent with literature values.[385]

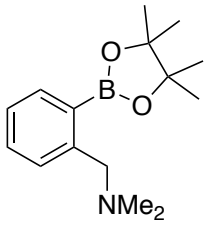
4,4,6,6-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborinane 9e



2-naphthylboronic acid (2.0 g, 11.6 mmol) and 1,3-propanediol (1.54 g, 11.6 mmol) were dissolved in anhydrous THF (70 mL). $MgSO_4$ (1.4 g, 11.6 mmol) was added to the solution which was refluxed for 6 hours. The mixture was filtered through a plug of cotton wool, concentrated *in vacuo*, purified by silica gel column chromatography (100 % pentane) and obtained as a white solid (2.9 g, 93 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.38 (s, 1H), 7.93-7.90 (m, 2H), 7.85-7.81 (m, 2H), 7.51-7.45 (m, 2H), 1.97 (s, 2H), 1.49 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 134.9, 134.9, 133.1, 130.3, 128.8, 127.8, 126.7, 126.5, 125.5, 71.1, 49.2, 32.0, (C-B not observed). ^{11}B NMR ($CDCl_3$, 160 MHz) δ 26.7 (br, s). MP 82-83 ^{o}C. IR (neat) υ/ cm^{-1} 684, 755, 823, 1198, 1305, 1368, 2979. HRMS (CI) calculated for $C_{17}H_{22}BO_2^+$ ($M+H^+$): 269.1707, observed: 269.1701.

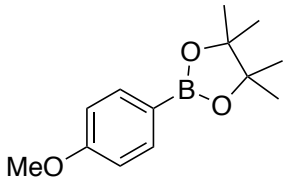
_N_,_N_-dimethyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine

9f



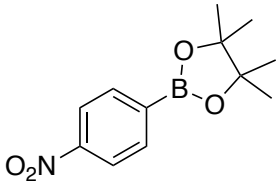
An oven dried flask was charged with $[Ir(\mu\text{-}OMe)(COD)]_2$ (20 mg, 1.5 mol%), 2-(aminomethyl)pyridine (6.2 mL, 3.0 mol%), B_2pin_2 (423 mg, 1.67 mmol), *N,N*-dimethylbenzylamine (301 mL, 2.00 mmol), and 4.0 mL of methylcyclohexane. After 16 h at 70 °C, the volatiles were removed *in vacuo*. Purification by flash column chromatography (98:1:1 CH_2Cl_2:MeOH:NEt_3) afforded the title compound as a white solid (413 mg, 79 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.53 (d, *J* = 6.7, 1H), 7.23-7.15 (m, 2H), 6.99 (d, *J* = 7.5, 1H), 3.84 (s, 2H), 2.55 (s, 6H), 1.30 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ , 139.8, 131.6, 127.6, 127.4, 123.1, 80.5, 65.6, 45.8, 26.7. (C-B not observed). Data consistent with literature values.[386]

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 9g



4-methoxyphenylboronic acid (3.5 g, 23.0 mmol) and pinacol (2.72 g, 23.0 mmol) were dissolved in anhydrous Et_2O (70 mL) and stirred at room temperature for 1 hour. The mixture was then concentrated *in vacuo* and the crude product purified by silica gel column chromatography (1/1 pentane/Et_2O) and obtained as a white solid (4.1 g, 76 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.76 (d, *J* = 8.7, 2H), 6.90 (d, *J* = 8.7, 2H), 3.83 (s, 3H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ , 162.3, 136.6, 113.4, 83.7, 55.2, 25.0, (C-B not observed). Data consistent with literature values.[387]

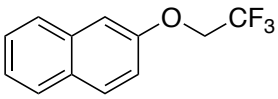
4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane 9h



4-nitrophenylboronic acid (1.28 g, 7.6 mmol) and pinacol (910 mg, 7.6 mmol) were dissolved in anhydrous Et_2O (25 mL) and stirred at room temperature for 1 hour. The mixture was then concentrated *in vacuo* and the crude product purified by silica gel column chromatography (1/1 pentane/Et_2O) and obtained as a white solid (1.8 g, 92 %). ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.19 (d, *J* = 8.7, 2H), 7.95 (d, *J* = 8.7, 2H), 1.36 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 149.9, 135.8, 122.5, 84.8, 25.0 (C-B not observed). Data consistent with literature values.[388]

4.3.2 Preparation of 2,2,2-trifluoroethoxy Arenes 13

2-(2,2,2-trifluoroethoxy)naphthalene 13a



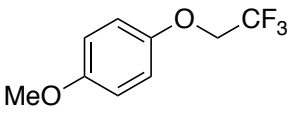
An oven-dried reaction flask, equipped with reflux condenser, was charged with $Cu(OAc)_2.H2O$ (9 mg, 10 mol%), DMAP (122 mg, 2.0 eq.), 2-naphthylboronic acid (86 mg, 1.0 eq.). The flask was then flushed three times with oxygen. Trifluoroethanol (3ml) was added and the reaction mixture was stirred at 40 ^{o}C for 1 hours. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel to remove the catalyst, DMAP and any insoluble byproducts, and the silica gel was washed with ethyl acetate. The solvent was concentrated *in vacuo* to afford the crude product which was purified by column chromatography (100 % pentane) and obtained as a white solid (77 mg, 68 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (d, *J* = 9.0, 2H), 7.75 (d, *J* = 8.2, 1H), 7.50-7.46 (m, 1H), 7.42-7.38 (m, 1H), 7.24-7.21 (m, 1H), 7.16 (d, *J* = 2.6, 1H), 4.48 (q, $^{3}J_{HF}$ = 8.1, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.4, 134.2, 130.1, 129.8, 127.9, 127.1, 126.9, 124.7, 123.5 (q, $^{1}J_{CF}$ = 278.8), 118.5, 107.6, 65.9 (q, $^{2}J_{CF}$ = 35.7). ^{19}F NMR ($CDCl_3$, 376 MHz) δ -73.8 (t, $^{3}J_{FH}$ = 8.0). Data consistent with literature values.[37]

General Procedure L

All reactions were performed on a 0.5 mmol scale unless stated otherwise. An oven-dried reaction flask, equipped with reflux condenser, was charged with copper catalyst (10 mol%), DMAP (61 mg, 1.0 eq.), aryl(hetero) boronic acid or boronic acid pinacol esters (0.5 mmol, 1.0 eq.). The flask was then flushed three times with oxygen. Trifluoroethanol (3ml) was added and the reaction mixture was stirred at 40 ^{o}C for 1 hour. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel to

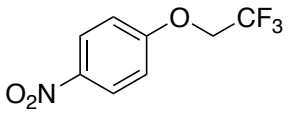
remove the catalyst, DMAP and any insoluble byproducts, and the silica gel was washed with ethyl acetate. The solvent was concentrated *in vacuo* to afford the crude product which was purified by column chromatography.

1-methoxy-4-(2,2,2-trifluoroethoxy)benzene 13c



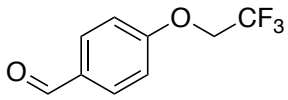
The title compound was prepared following general procedure L using 4-methoxyphenylboronic acid pinacol ester and $Cu(OAc)_2.H_2O$. Purified by silica gel column chromatography (100 % pentane to 1/1 pentane/CH_2Cl_2) and obtained as a colourless oil (50 mg, 48 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.89 (d, *J* = 9.1, 2H), 6.85 (d, *J* = 9.1, 2H), 4.30 (q, $^3J_{FH}$ = 8.2, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.2, 151.8, 123.5 (q, $^1J_{CF}$ = 276.6), 116.5, 114.9, 67.1 (q, $^2J_{CF}$ = 35.5) 55.8. ^{19}F NMR ($CDCl_3$, 377 MHz) δ -74.1 (t, $^3J_{FH}$ = 8.2). Data consistent with literature values.[37]

1-nitro-4-(2,2,2-trifluoroethoxy)benzene 13d



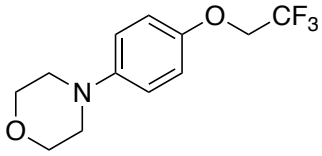
The title compound was prepared following general procedure L using 4-nitrophenylboronic acid pinacol ester and $Cu(OAc)_2.H_2O$. Purified by silica gel column chromatography (100 % pentane to 8/2 pentane/CH_2Cl_2) and obtained as a white solid (73 mg, 66 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.25 (d, $^3J_{HH}$ = 9.1, 2H), 7.04 (d, $^3J_{HH}$ = 9.1, 2H), 4.46 (q, $^3J_{FH}$ = 7.8, 2H).^{13}C NMR ($CDCl_3$, 101 MHz) δ , 161.9, 143.0, 126.2, 122.9 (q, $^1J_{CF}$ = 278.2), 115.0, 65.9 (q, $^2J_{CF}$ = 36.1). ^{19}F NMR ($CDCl_3$, 377 MHz) δ -73.7 (t, $^3J_{FH}$ = 7.9). Data consistent with literature values.[389]

4-(2,2,2-trifluoroethoxy)benzaldehyde 13f



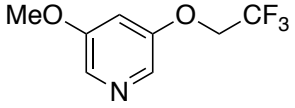
The title compound was prepared following general procedure L using 4-formylphenylboronic acid pinacol ester and $Cu(CF_3COO)_2.xH_2O$. Purified by silica gel column chromatography (100 % pentane to 8/2 pentane/Et_2O) and obtained as a colourless oil (75 mg, 73 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.92 (s, 1H), 7.88 (d, $^3J_{HH}$ = 8.2, 2H), 7.06 (d, $^3J_{HH}$ = 8.4, 2H), 4.44 (q, $^3J_{HF}$ = 7.9, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ , 190.7, 161.9, 132.2, 131.5, 123.1 (q, $^1J_{CF}$ = 277.7), 115.2, 65.7 (q, $^2J_{CF}$ = 36.1). ^{19}F NMR ($CDCl_3$, 377 MHz) δ -73.8 (t, $^3J_{FH}$ = 7.9). Data consistent with literature values.[390]

4-(4-(2,2,2-trifluoroethoxy)phenyl)morpholine 13e



The title compound was prepared following general procedure L using 4-morpholinophenylboronic acid pinacol ester and $Cu(CF_3COO)_2.xH_2O$. Purified by silica gel column chromatography (100 % pentane to 3/1 pentane/EtOAc) and obtained as a white solid (73 mg, 56 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.89 (s, 4H), 4.30 (q, $^3J_{HF}$ = 8.2, 2H), 3.86 (t, $^3J_{HH}$ = 4.7, 4H), 3.08 (t, $^3J_{HH}$ = 4.7, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 151.7, 147.2, 123.6 (q, $^1J_{CF}$ = 278.1), 117.6, 116.2, 67.1, 66.8 (q, $^2J_{CF}$ = 35.4) 50.4. ^{19}F NMR ($CDCl_3$, 377 MHz) δ -74.1 (t, $^3J_{FH}$ = 8.4). Data consistent with literature values.[391]

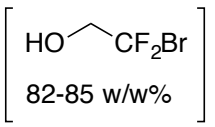
3-methoxy-5-(2,2,2-trifluoroethoxy)pyridine 13g



The title compound was prepared following a modified general procedure L (heating to 80 ^{o}C for 3 hours) using 5-methoxy3-pyridineboronic acid pinacol ester and $Cu(CF_3COO)_2.xH_2O$. Purified by silica

gel column chromatography (100 % CH_2Cl_2 to 3/1 CH_2Cl_2/EtOAc) and obtained as a white solid (69 mg, 67 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.04 (d, *J* = 37.5, 2H), 6.78 (s, 1H), 4.37 (q, $^3J_{HF}$ = 8.0, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ , 156.8, 154.7, 132.0, 129.3, 123.1 (q, $^1J_{CF}$ = 278.0), 108.1, 66.2 (q, $^2J_{CF}$ = 36.0) 55.9. ^{19}F NMR ($CDCl_3$, 377 MHz) δ -74.0 (t, $^3J_{FH}$ = 7.9). Data consistent with literature values.[389]

4.3.3 Preparation of 2-bromo-2,2-difluoroethanol 11



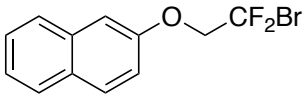
Adapted from procedure by Stephenson *et al*.[357] To a 3 L 3-necked RBF fitted with a dropping funnel was added sodium borohydride (10.3 g, 271 mmol, 1.1 eq.), tetrahydrofuran (450 mL) and water (25 mL) to give a heterogeneous solution. The solution was cooled with an ice/water bath and ethyl bromodifluouroacetate (50.0 g/31.6 mL, 246mmol, 1.0 eq.) in a solution of THF (250 mL) was added dropwise at approximately 2.5 ml/min upon which the solution became homogenous. (*Note in some instances the reaction became heterogeneous again with a white solid forming on the side of the flask. This can be made homogenous with the addition of a further minimum quantity of water*). At the end of the dropwise addition, the reaction was stirred for an additional 30 min until full consumption of starting material (followed by ^{19}F NMR). The solution was again cooled with an ice/water bath and 250 mL of 1N HCl was added dropwise maintaining the internal temperature at 15-20 °C and taking the solution to pH 2. 250 mL of Et_2O was added, the layers separated and the aqueous phase re-extracted with 100 mL of Et_2O. The combined organic phase was washed with 250 mL of sat $NaHCO_3$, 250 mL of saturated NaCl, dried with Na_2SO_4, filtered and concentrated at 40 °C and 100 mbar to give a colourless oil, typically as a 82 - 85% w/w solution in THF. (*Note the solution can be concentrated further however at the expense of yield due to the likely volatility of 11*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (td, $^3J_{HF}$ = 11.5 and $^3J_{HH}$ = 7.3, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 121.9 (t, $^1J_{CF}$ = 307.4), 68.8 (t, $^2J_{CF}$ = 26.8). ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3 (t, $^3J_{FH}$ = 11.5). Data consistent with literature values.[358] (*Note 11 was stored in a freezer under argon upon which time small quantities of white precipitate can form without apparent effect on the purity of 11*).

4.3.4 Preparation of 2-bromo-2,2-difluoroethoxy (hetero)Arenes 12

General Procedure M

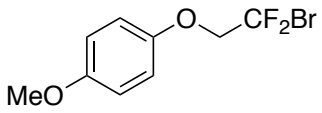
(Hetero) aryl pinacol boronic ester (0.25 mmol, 1.0 eq.), $Cu(CF_3COO)_2.xH_2O$ (10 mol%) and DMAP (0.25 mmol, 1.0 eq.) were added to an oven-dried Schlenk flask which was then vacuum purged with oxygen three times. Bromodifluoroethanol (0.8 mL) was added and the solution stirred at 40 ^oC for 1 h for aryl pinacol boronic esters or 80 ^oC for 3 h for heteroaryl pinacol boronic esters. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel to remove the catalyst, DMAP and any insoluble byproducts, and the silica gel was washed with ethyl acetate. The solvent was concentrated *in vacuo* to afford the crude product which was purified by column chromatography.

2-(2-bromo-2,2-difluoroethoxy)naphthalene 12a



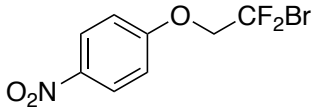
The title compound was prepared following general procedure M using naphthalene-2-boronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane) and obtained as a white solid (43 mg, 60 %). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.7, 2H), 7.75 (d, *J* = 8.2, 1H), 7.48 (t, *J* = 7.5, 1H), 7.40 (t, *J* = 7.6, 1H), 7.22 (d, *J* = 2.4, 1H), 7.18 (d, *J* = 2.1, 1H), 4.61 (t, $^3J_{HF}$ = 11.1, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.4, 134.3, 130.1, 129.9, 127.9, 127.1, 126.9, 124.7, 119.1 (t, $^1J_{CF}$ = 306.7), 118.5, 108.2, 72.9 (t, $^2J_{CF}$ = 27.0). ^{19}F NMR (377 MHz, $CDCl_3$): δ -56.12 (t, $^3J_{FH}$ = 11.1). MP 48-50 ^oC. IR (neat) υ/ cm^{-1} 653, 1072, 1255, 2889, 2981. HRMS (EI) Calculated for $C_{12}H_9BrF_2O^+$ (M^+): calculated 285.9805, observed 285.9801.

1-(2-bromo-2,2-difluoroethoxy)-4-methoxybenzene 12c



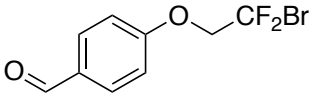
The title compound was prepared following general procedure M using 4-methoxyphenylboronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane to 98:2 pentane/Et_2O) and obtained as a colourless oil (112 mg, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.9, 2H), 6.85 (d, *J* = 9.0, 2H), 4.43 (t, $^3J_{HF}$ = 11.3, 2H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 151.9, 119.4 (t, $^1J_{CF}$ = 306.8), 116.9, 114.9, 74.3 (t, $^2J_{CF}$ = 26.3), 55.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ -56.3 (t, $^3J_{FH}$ = 11.3). IR (neat) υ/ cm^{-1} 823, 928, 1070, 1193, 1232, 1505, 2837, 2937. HRMS (EI)Calculated for $C_9H_9BrF_2O_2^+$ (M^+): calculated 265.9754, observed 265.9744.

1-(2-bromo-2,2-difluoroethoxy)-4-nitrobenzene 12d



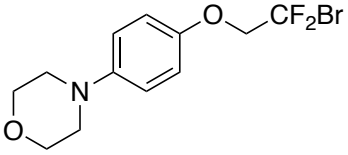
The title compound was prepared following general procedure M using 4-nitrophenylboronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane to 80/20 pentane/CH_2Cl_2) and obtained as a yellow oil (104 mg, 37 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.23 (m, 2H), 7.07-7.03 (m, 2H), 4.58 (t, $^3J_{HF}$ = 10.9, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9, 143.0, 126.2, 118.1 (t, $^1J_{CF}$ = 306.7), 115.2, 72.7 (t, $^3J_{CF}$ = 27.5). ^{19}F NMR (377 MHz, $CDCl_3$): δ -56.6 (t, $^3J_{FH}$ = 10.9). IR (neat) υ/ cm^{-1} 672, 764, 844, 928, 1070, 1111, 1259, 1342, 1495, 1514, 1592, 2890, 3087. HRMS (EI) Calculated for $C_8H_6BrF_2NO_3^+$ (M^+): calculated 280.9499, observed 280.9495.

4-(2-bromo-2,2-difluoroethoxy)benzaldehyde 12f



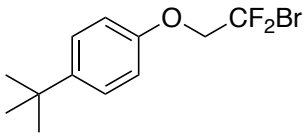
The title compound was prepared following general procedure M using 4-formylphenylboronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane to 80/20 pentane/Et_2O) and obtained as a white solid (125 mg, 47 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.91 (s, 1H), 7.87 (d, *J* = 8.9, 2H), 7.07 (d, *J* = 8.7, 2H), 4.57 (t, $^3J_{HF}$ = 11.0, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ , 190.7, 161.9, 132.1, 131.5, 118.4 (t, $^1J_{CF}$ = 306.6), 115.4, 72.5 (t, $^2J_{CF}$ = 27.6). ^{19}F NMR ($CDCl_3$, 470 MHz) δ -56.5 (t, $^3J_{FH}$ = 10.9). HRMS (EI) Calculated for $C_9H_7BrF_2O_2^+$ (M^+): calculated 263.9592, observed 263.9608. MP 48-49 °C. IR (neat) υ/ cm^{-1} 608, 747, 827, 949, 1074, 1111, 1126, 1255, 1598, 1692.

4-(4-(2-bromo-2,2-difluoroethoxy)phenyl)morpholine 12e



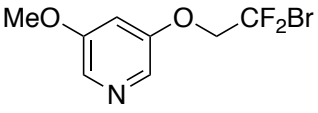
The title compound was prepared following general procedure M using 4-morpholinophenylboronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane to 3/1 pentane/EtOAc) and obtained as a white solid (167 mg, 52 %). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.92 (d, *J* = 9.3, 2H), 6.88 (d, *J* = 9.3, 2H), 4.43 (t, $^3J_{HF}$ = 11.3, 2H), 3.86 (t, $^3J_{HH}$ = 4.8, 4H), 3.08 (t, $^3J_{HH}$ = 4.8, 4H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.8, 147.3, 119.5 (t, $^1J_{CF}$ = 307.2), 117.6, 116.6, 74.0 (t, $^2J_{CF}$ = 26.4), 67.1, 50.5. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -56.2 (t, $^3J_{FH}$ = 11.3). MP 69-70 °C. HRMS (EI) Calculated for $C_{12}H_{14}BrF_2NO_2^+$ (M^+): calculated 321.0170, observed 321.0177. IR (neat) υ/ cm^{-1} 655, 814, 934, 1070, 1116. 1175, 1246, 1382, 1510, 2889, 2890.

1-(2-bromo-2,2-difluoroethoxy)-4-(*tert*-butyl)benzene 12b



The title compound was prepared following general procedure M using 4-*tert*-butylphenylboronic acid pinacol ester. Purified by silica gel column chromatography (100 % pentane) and obtained as a yellow oil (31 mg, 41 %). ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.34 (d, *J* = 8.9, 2H), 6.90 (d, *J* = 8.9, 2H), 4.47 (t, $^{3}J_{HF}$ = 11.2, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 145.6, 126.7, 119.4 (t, $^{1}J_{CF}$ = 305.1), 115.0, 73.3 (t, $^{2}J_{CF}$ = 26.9), 34.4, 31.6. ^{19}F NMR ($CDCl_3$, 377 MHz) δ -56.4 (t, $^{3}J_{FH}$ = 11.2). IR (neat) υ/ cm^{-1} 2963, 2871, 1608, 1512, 1249, 1182, 1072, 926, 828, 770, 648. HRMS (EI) Calculated for $C_{12}H_{15}BrF_2O^+$ (M^+): calculated 292.0269, observed 292.0268.

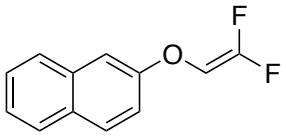
3-(2-bromo-2,2-difluoroethoxy)-5-methoxypyridine 12g



The title compound was prepared following a modified general procedure M (heating to 80 °C for 3 hours) using 5-methoxy-3-pyridineboronic acid pinacol ester. Purified by silica gel column chromatography (100 % CH_2Cl_2 to 3/1 CH_2Cl_2/EtOAc) and obtained a yellow oil (65 mg, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.98 (s, 1H), 6.82 (s, 1H), 4.52 (t, $^{3}J_{HF}$ = 11.0, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ , 156.8, 154.6, 132.0, 129.7, 118.5 (t, $^{1}J_{CF}$ = 306.7), 108.4, 73.2 (t, $^{2}J_{CF}$ = 27.2), 56.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.6 (t, $^{3}J_{FH}$ = 11.1). HRMS (ESI) Calculated for $C_8H_9BrF_2NO_2^+$ ($M+H^+$): calculated 267.9779, observed 267.9780. IR (neat) υ/ cm^{-1} 653, 700, 921, 1071, 1134, 1167, 1304, 1429, 1588, 2889, 2972.

4.3.5 Preparation of (2,2-difluorovinyl)oxy Arenes 14

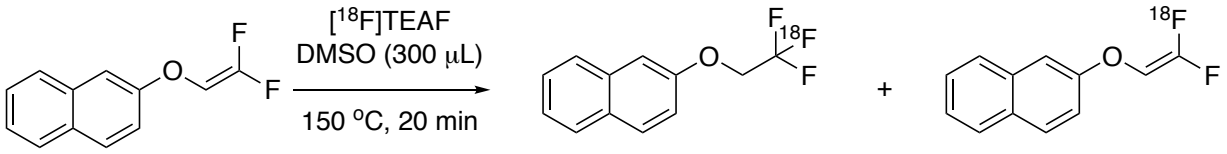
2-((2,2-difluorovinyl)oxy)naphthalene 14a



An oven-dried Schlenk was charged with naphthalene-2-boronic acid pinacol ester (64 mg, 0.25 mmol, 1.0 eq.), $Cu(CF_3COO)_2.xH_2O$ (10 mol%) and 4-dimethyaminopiridine (31 mg, 1.0 eq.). The vessel was then vacuum purged with O_2 three times and charged with 2-bromo-2,2-difluoroethanol **11** (0.8 mL). The resulting solution was then stirred vigorously at 40 ^{o}C until complete consumption of aryl boronate ester was observed by TLC (typically 1-2 hours). The reaction mixture was diluted with ethyl acetate (0.5 mL) and filtered through a short plug of silica. The resulting filtrate was concentrated under reduced pressure to remove excess 2-bromo-2,2-difluoroethanol (typically <20 mbar at 60 ^{o}C on a rotary evaporator). The residue was dissolved in acetonitrile (1.0 mL) and solid NaOH (3.0 eq.) was added. A minimum amount of water was added to solubilize the NaOH and the reaction stirred at 50 ^{o}C for 16 h. Once the reaction was deemed to be complete by TLC the product was extracted with ethyl acetate and purified by column chromatography (100% pentane) to yield the title compound as a white solid (26 mg, 51 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, *J* = 8.9, 2H), 7.77 (d, *J* = 8.2, 1H), 7.50 (t, *J* = 7.5, 1H), 7.42 (t, *J* = 7.5, 1H), 7.31 (s, 1H), 7.26 (dd, *J* = 8.9, 2.3, 1H), 6.22 (dd, $^{3}J_{HF}$ = 15.2 and $^{3}J_{HF}$ = 3.4, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 157.0 (dd, $^{1}J_{CF}$ = 290.9 and $^{1}J_{CF}$ = 278.1), 155.2, 134.2, 130.1, 127.9, 127.2, 127.0, 124.8, 117.9, 109.3, 104.6 (dd, $^{2}J_{CF}$ = 56.3 and $^{2}J_{CF}$ = 15.0). ^{19}F NMR ($CDCl_3$, 377 MHz) δ , -97.0 (dd, $^{2}J_{FF}$ = 67.5 and $^{3}J_{FH}$ = 15.2), -115.2 (dd, $^{2}J_{FF}$ = 67.8 and $^{3}J_{FH}$ = 3.1). M.p. 49-51 ^{o}C. IR (neat) υ/ cm^{-1} 624, 755, 820, 851, 928, 1180, 1215, 1238, 1337, 1772, 3066. HRMS (CI) Calculated for $C_{12}H_9F_2O^+$ ($M+H^+$): calculated 207.0616, observed 207.0619.

4.3.6 General Information for Radiochemical Procedures

Substrate **14a** (0.04 mmol) was added to v-vial containing stirrer bar. Fluoride, DMSO (300 μL) (and additive, if applicable) were added. The reaction mixture was heated at 150 ^{o}C for 20 minutes before it was quenched with 200 μL of water. An aliquot of the crude mixture was analysed by radio TLC and radio HPLC.



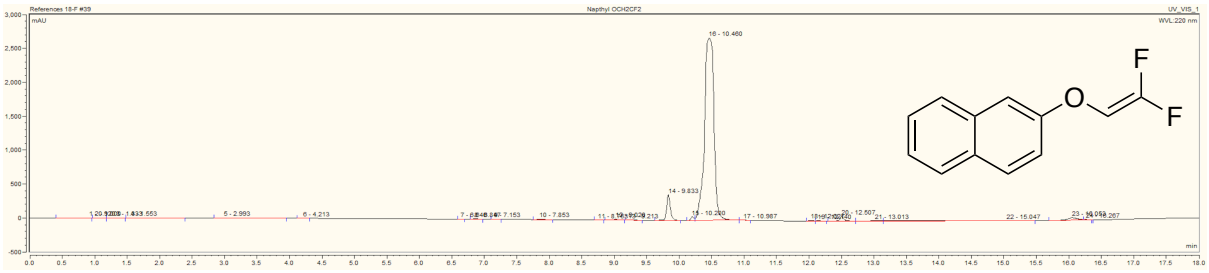
14a **[^{18}F]13a** **[^{18}F]14a**

Entry	Additive	RCC [^{18}F]13a/ %	RCC RCC [^{18}F]14a / %
1	-	0	89 ± 1 % (n = 2) (RCP = 98 ± 1 %)
2	TBAF (2.0 eq.)	55 ± 17 % (n = 2) (RCP = 97 ± 1 %)	0

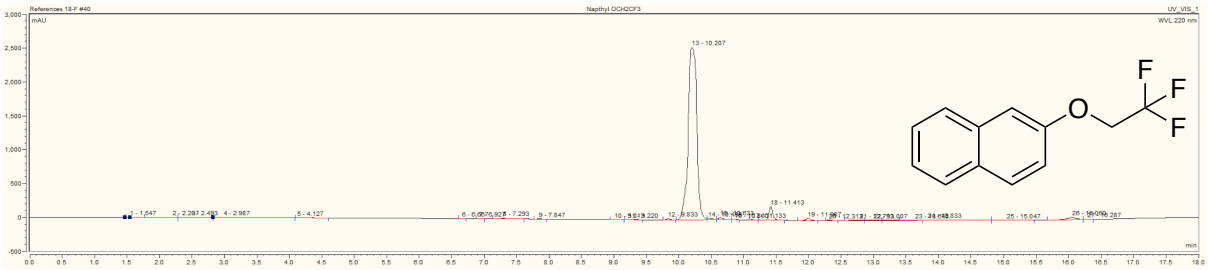
Labelling experiments conducted at the Siemens Oxford Molecular Imaging Laboratory (SOMIL) by Thomas Wilson and Jeroen Sap.

4.3.7 Authentic UV References and Radio-HPLC traces

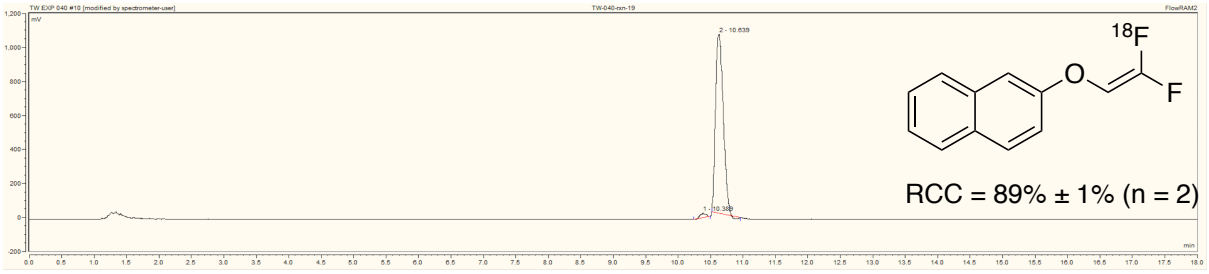
2-((2,2-difluorovinyl)oxy)naphthalene 14a



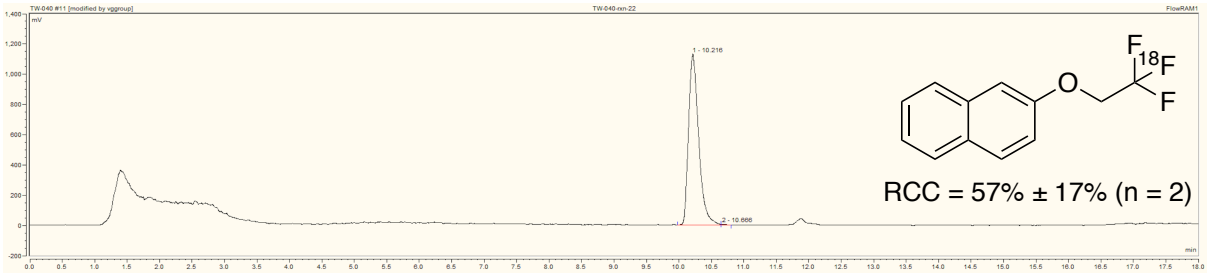
2-(2,2,2-trifluoroethoxy)naphthalene 13a



[^{18}F]2-((2,2-difluorovinyl)oxy)naphthalene [^{18}F]14a (n.c.a.)



[^{18}F] 2-(2,2,2-trifluoroethoxy)naphthalene [^{18}F]13a (c.a.)



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5.0 REFERENCES

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Carbenes

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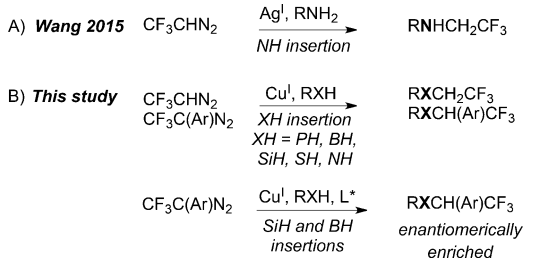
Copper-Catalyzed Insertion into Heteroatom–Hydrogen Bonds with Trifluorodiazoalkanes

*Stephen Hyde, Janis Veliks, Benoît Liégault, David Grassi, Marc Taillefer, and Véronique Gouverneur**

Abstract: *Copper-catalyzed Si–H, B–H, P–H, S–H, and N–H insertion reactions of 2,2,2-trifluoro-1-diazoethane and 1-aryl 2,2,2-trifluorodiazoethanes generated a large number of new fluorine-containing chemical entities for medicinal chemists. With selected Si–H and B–H insertion reactions, we demonstrate successful extension to asymmetric catalysis.*

The wide range of materials and biologically active molecules containing fluorine substitution has prompted much research on late-stage fluorination and trifluoromethylation.[1] The installation of a 1,1,1-trifluoro-2λ^3-ethane (CF_3CH_2) fragment onto arenes and heteroatoms has received less attention. Recent developments include cross-coupling reactions with CF_3CH_2I under Pd catalysis with aryl boronic acids,[2] or through CH arene functionalization.[3] More conventional approaches have been implemented for heteroatom trifluoroethylation: The N-trifluoroethylation of anilines with an electrophilic hypervalent iodine CH_2CF_3 reagent has been reported;[4] alternatively, trifluoroacetaldehyde has been subjected to reductive amination.[5] The installation of branched trifluoroalkyl fragments of the type CF_3CHR is more challenging, especially when enantioselectivity is required. With heteroatom functionalization as our primary objective, we opted to address this problem with a strategy based on heteroatom–hydrogen bond (X–H) insertion. Transition-metal-catalyzed X–H (X = O, N, S, Si, B) insertions of diazo compounds are a powerful approach for the construction of C–X bonds.[6] This methodology has been studied extensively with α-diazoesters and α-diazoketones, and extended to numerous asymmetric carbene-insertion reactions. The attractive synthetic route towards 2,2,2-trifluorodiazoethane (CF_3CHN_2) reported by Morandi and Carreira[7] led us to consider this class of CF_3-containing synthon in the context of X–H insertion. This choice was driven by the prospect of extending this methodology to asymmetric carbene insertion with 1-aryl 2,2,2-trifluorodiazoethanes.[8] Wang and co-workers recently reported the trifluoroethylation of anilines and amides with 2,2,2-trifluorodiazoethane under Ag^I catalysis; this catalytic system was applied exclusively to insertion reactions involving amines and amides, and does not offer a platform towards asymmetric catalysis since the products of trifluoroethylation are achiral (Scheme 1 A).[9] Herein, we report that Si–H, B–H, P–H, S–H, and N–H insertion reactions of trifluorodiazoalkanes are possible under Cu^I catalysis; asymmetric variants are reported for selected Si–H and B–H insertions. The insertion products expand the chemical space available to chemists (Scheme 1 B).



Scheme 1. Silver- and copper-catalyzed X–H bond insertion reactions with trifluorodiazoalkanes.

This study began with the preparation of 2,2,2-trifluoro-1-diazoethane (**1a**) from commercially available $CF_3CH_2NH_2{\cdot}HCl$ by the procedure disclosed by Morandi and Carreira.[7] The body of work on copper-[10] and rhodium-catalyzed[11] X–H insertion with α-diazoesters prompted us to focus on these transition metals to probe the reactivity of 2,2,2-trifluoro-1-diazoethane with the model substrate dimethylphenylsilane (Table 1).

Optimization studies indicated that $[Cu(CH_3CN)_4]PF_6$ was superior to $[Rh_2(OAc)_4]$ for Si–H bond insertion in either dichloromethane or 2,2-dimethylbutane (DMB) as the reaction solvent (Table 1, entries 1–4). Slow addition (30 min) of the diazo reagent to a solution of the silane and catalyst led to significant improvement by suppressing the side reaction resulting from diazo dimerization (Table 1, entry 5). A catalyst loading of 2 mol% was effective, but the product was formed in lower yield when it was decreased to 1 mol% (Table 1, entries 7 and 9). With this slow-addition protocol in place, $[Cu(CH_3CN)_4]PF_6$ (2 mol%) was retained for further studies as superior to $Cu(OTf)_2$ (Table 1, entries 8). No reaction took place with $AgSbF_6$ (5 mol%) in 1,2-dichloroethane (DCE; Table 1, entry 10); these reaction conditions were identified as optimal for the N-trifluoroethylation of

[*] S. Hyde, Dr. J. Veliks, Dr. B. Liégault, Dr. D. Grassi, Prof. V. Gouverneur
University of Oxford, Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: veronique.gouverneur@chem.ox.ac.uk
Dr. B. Liégault, Dr. M. Taillefer
Institut Charles Gerhardt Montpellier
UMR-CNRS 5253, AM2N, ENSCM
8 rue de l'Ecole Normale, 34296 Montpellier Cedex 5 (France)

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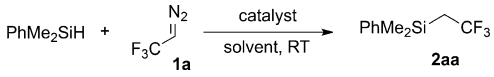
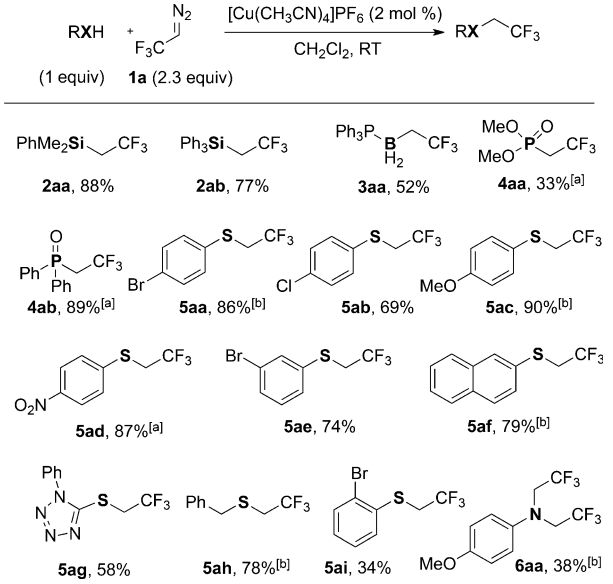
Table 1: Evaluation of reaction conditions for Si–H insertion.[a]



Entry	Catalyst (mol%)	Conditions[b]	Solvent	Yield [%][c]
1	$[Rh_2(OAc)_4]$ (5)	A	CH_2Cl_2	16
2	$[Rh_2(OAc)_4]$ (5)	A	DMB	15
3	$[Cu(CH_3CN)_4]PF_6$ (5)	A	CH_2Cl_2	44
4	$[Cu(CH_3CN)_4]PF_6$ (5)	A	DMB	34
5	$[Cu(CH_3CN)_4]PF_6$ (5)	B	CH_2Cl_2	87
6	$[Cu(CH_3CN)_4]PF_6$ (5)	B	toluene	61
7	$[Cu(CH_3CN)_4]PF_6$ (2)	B	CH_2Cl_2	(88)
8	$Cu(OTf)_2$ (2)	B	CH_2Cl_2	32
9	$[Cu(CH_3CN)_4]PF_6$ (1)	B	CH_2Cl_2	61
10[d]	$AgSbF_6$ (5)	B	DCE	0
11	–	B	CH_2Cl_2	0
12	$[Cu(CH_3CN)_4]PF_6$ (2)	B	CH_2Cl_2	(77)[e]

[a] Reaction conditions: $PhMe_2SiH$ (1.0 equiv), **1a** (2.3 equiv). [b] Conditions A: manual addition of **1a**; conditions B: slow addition of **1a** over 0.5 h with a syringe pump. [c] The yield was determined by ^{19}F NMR spectroscopy with trifluorotoluene as an internal reference. Values in parenthesis indicate the yield of the isolated product. [d] The reaction was performed at 60 °C. [e] The reaction was performed with triphenylsilane. The product is triphenyl(2,2,2-trifluoroethyl)silane (**2ab**).



Scheme 2. Copper-catalyzed Si–H, B–H, P–H, S–H, and N–H bond insertion with 2,2,2-trifluoro-1-diazoethane (**1a**). Reaction conditions: Slow addition of **1a**, then stirring for 18 h at room temperature. Yields given are for the isolated product. [a] The reaction was performed with $NaBAr_F$ (2.2 mol%). [b] $[Cu(CH_3CN)_4]PF_6$: 4 mol%.

anilines and amides.[9] As expected, the catalyst was essential for Si–H insertion (Table 1, entry 11). The optimal reaction conditions therefore consist of treating dimethylphenylsilane with an excess of the diazo reagent (2.3 equiv) in dichloromethane at room temperature in the presence of $[Cu(CH_3CN)_4]PF_6$ (2 mol%) for 18 h. Under these conditions, the product of Si–H insertion **2aa** was isolated in 88% yield (Table 1, entry 7). Pleasingly, Si–H insertion of more sterically demanding triphenylsilane was also successful and led to product **2ab** in 77% yield (Table 1, entry 12).

After establishing these conditions for copper-catalyzed Si–H insertion with 2,2,2-trifluoro-1-diazoethane (**1a**), we examined the reactivity of triphenylphosphine-protected borane, dimethyl phosphonate, diphenylphosphine oxide, thiols, and 4-methoxyaniline, and found that the generality of the heteroatom–hydrogen insertion process is striking (Scheme 2). Triphenylphosphine borane is a suitable substrate and was converted into the B–H insertion product **3aa** in 52% yield. Dimethyl phosphonate and diphenylphosphine oxide also reacted under Cu^I catalysis to afford **4aa** and **4ab** in 33 and 89% yield, respectively, thereby establishing the feasibility of P–H insertion. The reaction tolerates a range of aryl, heteroaryl, and alkyl thiols, thus leading to the 2,2,2-trifluoroethyl-substituted sulfides **5aa–ah** in up to 90% yield. Under the standard reaction conditions, the reaction of 2,2,2-trifluoro-1-diazoethane with 4-methoxyaniline led to the product of double insertion **6aa**. The product of the O–H insertion of phenol was not observed with either $[Cu(CH_3CN)_4]PF_6$ or $AgSbF_6$.

The broad scope of this method encouraged further studies on the installation of branched trifluoroalkyl fragments. We probed the reactivity of the model 1-aryl 2,2,2-trifluoro-1-diazoethanes **1b–f**[8] in a range of heteroatom–hydrogen insertion reactions. For this class of diazoethanes, the reaction was performed with an excess of the nucleophilic component, and the catalyst loading was typically increased to 4 mol% (Scheme 3).

The reaction scope is very broad, and a large collection of novel chiral products with a CF_3 substituent located at the benzylic position were synthesized. Similarly to the reactions with 2,2,2-trifluoro-1-diazoethane (**1a**), Si–H, B–H, and P–H insertion reactions were feasible; the corresponding products were isolated in 61–98% yield. A detailed investigation of S–H insertion reactions revealed that aryl, heteroaryl, primary, secondary, and tertiary alkyl groups are all tolerated on the sulfur atom. Only strongly electron donating (OMe) or electron withdrawing (NO_2) groups located in the *para* position of benzenethiol are not compatible. All 1-aryl 2,2,2-trifluoro-1-diazoethanes tested were competent substrates with the exception of the nitro-substituted derivative **1f**. For the parent benzenethiol, we found that $[Cu(CH_3CN)_4]PF_6$ was superior to $[Cu(CH_3CN)_4]BAr_F$, and $AgSbF_6$ was not effective. In contrast to the product outcome observed with 2,2,2-trifluoro-1-diazoethane (**1a**), aniline derivatives underwent monoinsertion with no detectable products resulting from undesired double insertion. Primary alkyl and cycloalkyl amines also reacted with **1b** as demonstrated with the synthesis of **6be** and **6bf**, which were isolated in 40% and 92% yield, respectively. For reactions with **1b** leading to lower yields, 1-[(1,1′-biphenyl)-4-yl]-2,2-difluoroethan-1-one was the main side product isolated after work-up; this observation indicates that hydrolysis of the unreacted diazo precursor occurs to afford 1-[(1,1′-biphenyl)-4-yl]-2,2,2-trifluoroethan-1-ol, an intermediate prone to HF elimination.

The ability of $[Cu(CH_3CN)_4]PF_6$ to catalyze efficiently a range of heteroatom–hydrogen insertion reactions led us to carry out a series of competition experiments with the diazo

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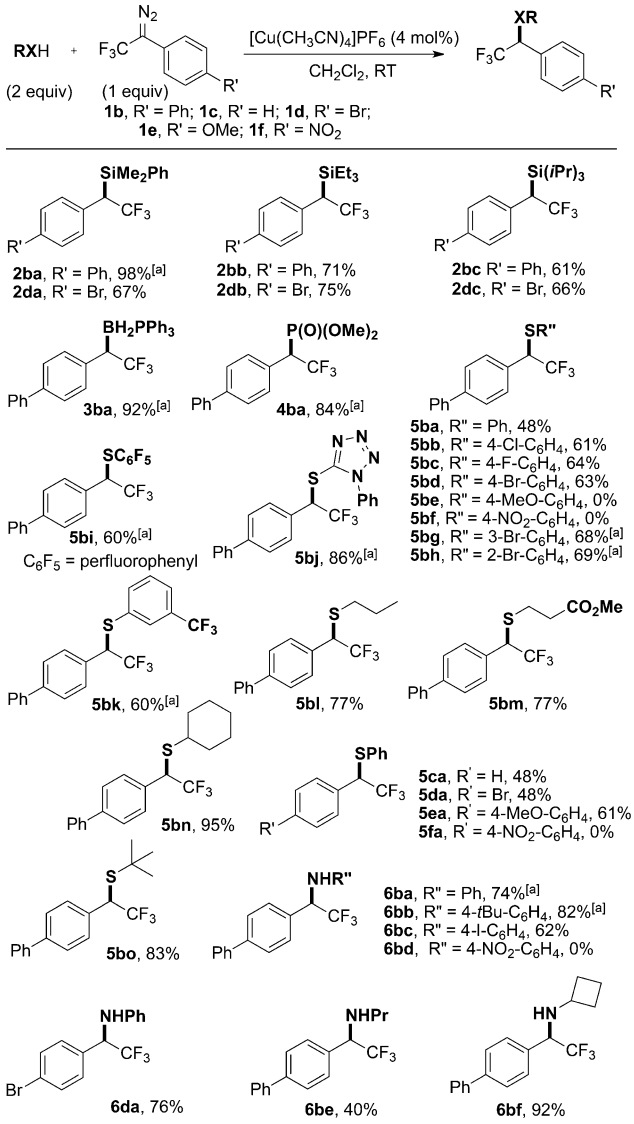
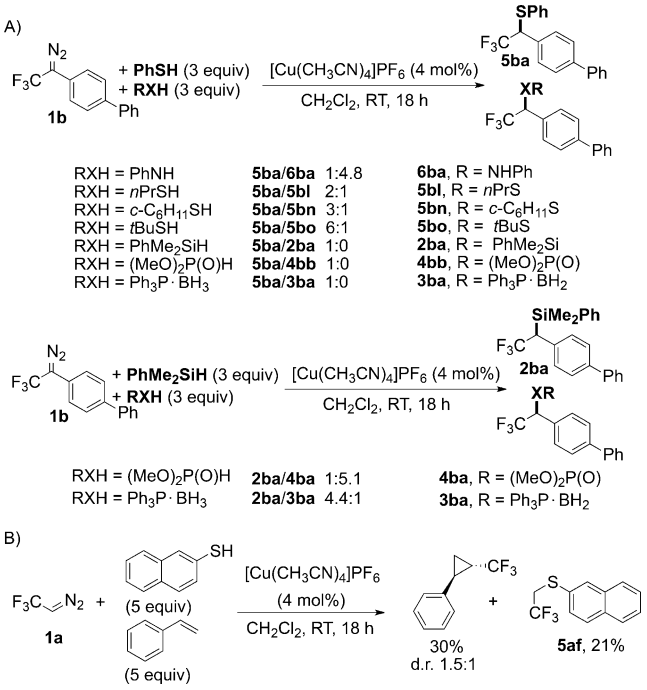


Scheme 3. Copper-catalyzed Si–H, B–H, P–H, S–H, and N–H bond insertion reactions with 1-aryl 2,2,2-trifluoro-1-diazoethanes **1b–f**. Reaction conditions: Slow addition of **1b–f** over 1 h, then stirring for 18 h at room temperature. [a] $[Cu(CH_3CN)_4]PF_6$: 2 mol%. Yields given are for the isolated product.

compound **1b** to provide an order of reactivity: $PhNH_2$ > PhSH > *n*PrSH > cyclohexylSH > *t*BuSH > $Ph_3P{\cdot}BH_3$ > Me_2PhSiH > $(MeO)_2P(O)H$. This ranking may serve as a predictive tool for insertion when substrates possessing two or more heteroatom–hydrogen functionalities are used (Scheme 4 A). The reaction of 2,2,2-trifluoro-1-diazoethane (**1a**) with an excess of naphthalene-2-thiol and styrene under Cu^I catalysis gave products of cyclopropanation[7] and S–H insertion (Scheme 4 B). In the absence of the thiol, the cyclopropane product was obtained in 96% yield; these experiments indicate the relevance of a donor–acceptor copper carbenoid species in the catalytic cycle. In contrast, the system reported by Wang and co-workers for silver-catalyzed N–H insertion with **1a**[9] afforded no product of cyclopropanation in the presence of styrene.



Scheme 4. Competition experiments. A) Copper-catalyzed Si–H, B–H, P–H, and N–H insertion versus PhS–H insertion with **1b**, and copper-catalyzed B–H and N–H insertion versus Si–H insertion with **1b**. The product ratio was determined by ^{19}F NMR spectroscopy. B) Cyclopropanation versus S–H bond insertion with **1a**. The yield was determined by ^{19}F NMR spectroscopy with 3-fluoronitrobenzene as an internal reference. Reaction conditions: Slow addition of **1a,b**, then stirring for 18 h at room temperature.

Asymmetric insertion reactions of diazoesters are well-documented,[12] and numerous reaction parameters as well as the nature of the ester group can influence enantioselectivity.[12c] To date, no catalytic enantioselective heteroatom–hydrogen insertion reactions are known for 2,2,2-trifluorodiazoethanes. The steric bulk of the trifluoromethyl group (A value: 2.1 kcal mol^{-1}) is similar to that of the isopropyl group (A value: 2.2) and larger than that of most ester functionalities (A value for CO_2Me: 1.3),[13] and the Hammett substituent constants[14] are in the same range as CF_3 (σ_{meta} = 0.43 and σ_{para} = 0.54) and CO_2Et (σ_{meta} = 0.37 and σ_{para} = 0.45); these trends encouraged exploratory studies with **1b** and **1d**, two diazo entities that are precursors of donor–acceptor-substituted metal carbenoids. The preference for copper complexes to remain bound to the substrate during protonation prompted the use of copper over rhodium complexes for asymmetric insertion reactions. Our research on the merging of organosilane and fluorine chemistry[15] led us to focus on Si–H insertion, as we anticipated that the nonpolar Si–H bond would favor a concerted mechanism for carbenoid insertion.[6,16] The resulting enantiomerically enriched products would be challenging to prepare by other routes (Scheme 5).

Experiments undertaken with a catalytic amount of $[Cu(CH_3CN)_4]PF_6$ (4 mol%) and the large noncoordinating ion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F^-,[17] 5 mol%) identified the chiral bisoxazoline Zhou ligand

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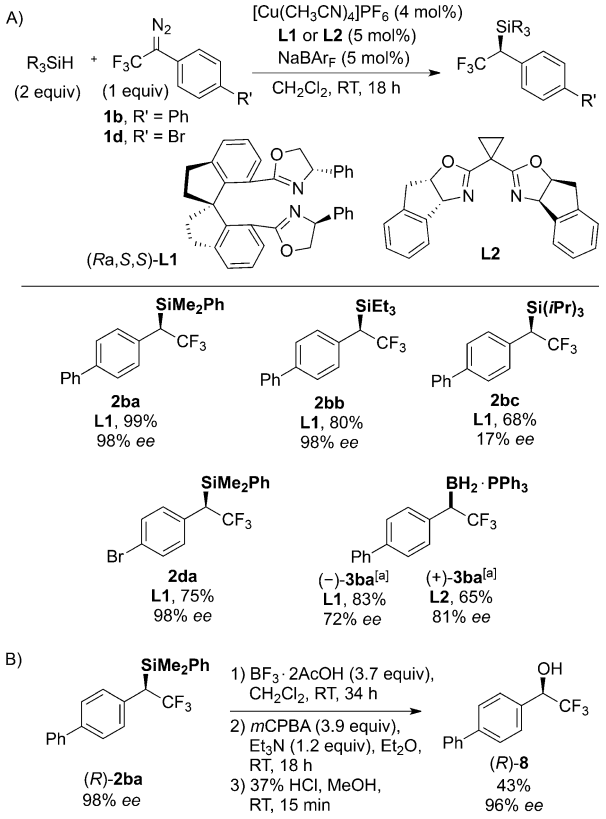

Scheme 5. Copper-catalyzed enantioselective Si–H and B–H insertion reactions with **1b** and **1d**. Reaction conditions: Slow addition of **1b** or **1d**, then stirring for 18 h at room temperature. Yields given are for the isolated product. [a] The reaction was performed with $Ph_3P{\cdot}BH_3$ (2 equiv). *m*CPBA = *m*-chloroperbenzoic acid.

(*R*a,*S*,*S*)-**L1** (5 mol%) based on the spirobiindane scaffold as optimal for the induction of high enantioselectivity.[18] With this ligand, Si–H insertion in dichloromethane at 25 °C with dimethylphenylsilane and triethylsilane afforded enantiomerically enriched (−)-**2ba** and (−)-**2bb**, which were isolated in 99 and 80% yield, respectively, with 98% *ee*. The diazo precursor **1d** was converted into (−)-**2da** in 75% yield with 98% *ee*. The yield and enantioselectivity decreased significantly with bulkier triisopropylsilane. The bisoxazoline **L2** was superior to **L1** for B–H insertion as exemplified by the synthesis of enantiomerically enriched (+)-**3ba** (81% *ee*) (Scheme 5A). For completion, we assigned the absolute configuration of **2ba** as *R* by performing a stereoretentive Tamao–Fleming oxidation[19] and comparing the $[\alpha]_D$ value of the resulting enantiomerically enriched alcohol (*R*)-**8** (*ee* > 96%) with a previously reported value (Scheme 5B).[20] The absolute configuration of other Si–H insertion products was tentatively assigned by analogy with (*R*)-**2ba**.

In summary, we have developed a catalytic insertion of 1-aryl 2,2,2-trifluoro-1-diazoalkanes into Si–H, B–H, P–H, S–H, and N–H bonds. These transformations enable the synthesis of a large collection of novel and valuable chiral CF_3-substituted molecules. Enantioselective Si–H and B–H insertion reactions catalyzed by Cu^I complexes derived from chiral bisoxazoline ligands proceeded in high yields with good to excellent enantioselectivity. Further study on the application of these novel reactions is ongoing in our laboratory.

Experimental Section

General procedure: $[Cu(CH_3CN)_4]PF_6$ (2–4 mol%) and the substrate (0.2 mmol, 2.0 equiv) were dissolved in degassed CH_2Cl_2 (0.5 mL). A solution of the $CF_3C(R)N_2$ reagent (0.1 mmol, 1.0 equiv) in CH_2Cl_2 (0.8 mL) was then added at room temperature over 1 h with a syringe pump, and the reaction mixture was stirred for 18 h. Once the reaction was complete (TLC), the solvent was evaporated, and the residue was purified by silica-gel column chromatography.

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Enantioselective rhodium-catalysed insertion of trifluorodiazoethanes into tin hydrides

Stephen Hyde [a], Janis Veliks [a], David M.H. Ascough [a], Robert Szpera [a], Robert S. Paton [a, b], Véronique Gouverneur [a, *]

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, OX1 3TA, UK
[b] Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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ABSTRACT

Aryl substituted 2,2,2-trifluorodiazoethanes undergo rhodium(II)-catalysed insertion reactions with tin hydrides affording the corresponding α-(trifluoromethyl)benzyl stannanes. This reactivity contrasts with that of diazo esters which predominantly afford CH_2 reduction products in the presence of tin hydrides. The first example of asymmetric insertion into tin hydrides using diazo compounds is also described. In addition, this system extends to asymmetric germanium hydride and silane insertion.

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1. Introduction

The insertion of diazo compounds into carbon-hydrogen and heteroatom-hydrogen bonds is well-documented [1–4]. Insertion reactions where X-H (X = C, Si, S, O, N, B, P) bonds are cleaved by Rh, Cu, or other metal carbenoid intermediates, have been well studied both in racemic [5–11] and asymmetric [12,13] settings. Insertion into trialkyltin hydrides has received relatively little attention, despite several early reports supporting the feasibility of such insertion with carbenes [14–16]. In 1995, Landais and co-workers reported an isolated example of trialkyltin hydride insertion with diazo esters (Fig. 1a) [17]. Wang later showed that tin hydride enables the reduction of diazo carbonyl compounds, a process resulting from *in situ* protodestannylation of the tin hydride insertion product (Fig. 1b) [18]. More recently, the groups of Wang and Bi have disclosed insertion into the Sn–H bond leading to stable benzyltributylstannanes [19,20]. Both methods generate the diazo intermediate *in situ* from a tosyl- or nosylhydrazone, however neither system offers a route to asymmetric insertion (Fig. 1c and d). Our group extended X-H insertion to trifluorodiazoalkanes [21]. Under Cu catalysis, Si–H, S–H, N–H, B–H, and P–H bonds were successfully cleaved, and an asymmetric protocol was developed for silanes and boranes (Fig. 1e). However, tributyltin hydride gave a low yield of the insertion product under our standard reaction conditions. Herein, we report the successful development of a rhodium catalysed tributyltin hydride insertion with aryl-substituted 2,2,2-trifluorodiazoethanes, as well as extension to an asymmetric catalytic protocol (Fig. 1f). This system is also suitable for asymmetric insertion into germanium hydrides and silanes.

2. Results and discussion

The starting materials for this study, aryl-substituted 2,2,2-trifluorodiazoethanes, were prepared according to previously reported literature procedures [22,23]. Optimization studies of the tributyltin hydride insertion reaction were performed using 4-(1-diazo-2,2,2-trifluoroethyl)-1,1′-biphenyl (**1a**) as the model substrate (Table 1). Under our previously reported conditions [21], involving slow addition over one hour of diazo compound to a mixture of $Cu(MeCN)_4PF_6$ (4 mol%) and tributyltin hydride (2 equivs), only 26% of the desired product **2a** was obtained, in addition to the reduced product (Table 1, entry 1). Decreasing the amount of nBu_3SnH to 1.0 equivalent and changing the order of addition were not beneficial (Table 1, entries 2 and 3). Under

* Corresponding author.
E-mail address: veronique.gouverneur@chem.ox.ac.uk (V. Gouverneur).

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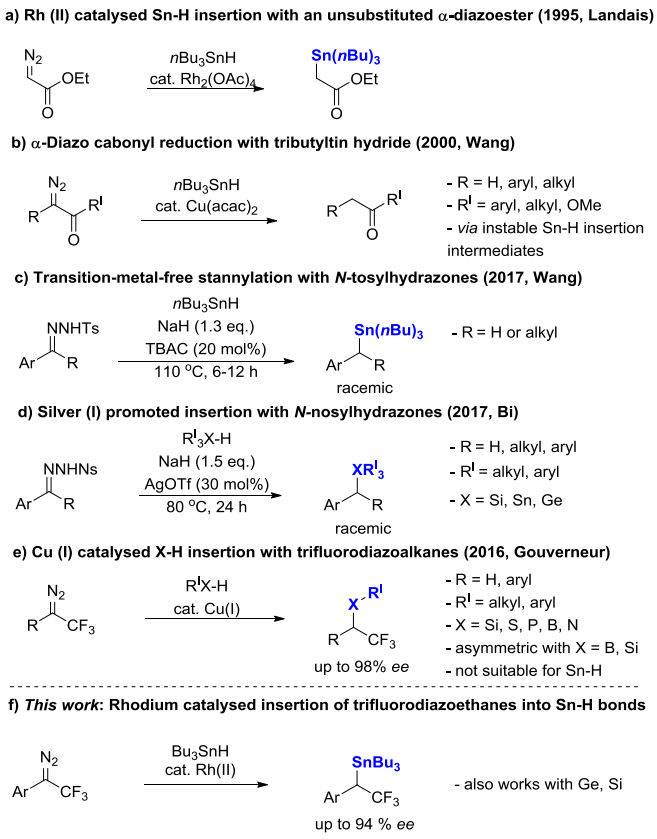


Fig. 1. Sn–H insertion reactions with trialkyltin hydrides.

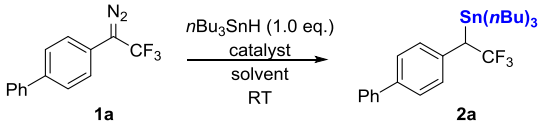
$Rh_2(OAc)_4$ catalysis, comparably poor results were obtained (entry 4). When the reaction was performed by fast addition of Rh(II) catalyst to an equimolar mixture of diazo compound **1a** and nBu$_3$SnH in dichloromethane in an open vial, almost instantaneous evolution of nitrogen and disappearance of the characteristic orange colour of the diazo compound **1a** was observed (Table 1, entry 5). The desired insertion product **2a** was isolated in 64% yield. Cu(II) and Rh(I) were ineffective for this transformation (entries 6 and 7). Screening various solvents highlighted dichloromethane as the optimum solvent for Sn–H insertion (entry 5 vs. entries 8–11).

When the reaction was performed under an argon atmosphere with degassed dichloromethane, and the reagent mixture quickly transferred to the catalyst under inert atmosphere, the yield of the desired product **2a** was further improved to 74% (entry 12). The use of 4 mol% of $Rh_2(OAc)_4$ was optimal for this transformation (entry 12 vs. 13 and 14).

After optimization of the reaction conditions, the substrate scope was investigated (see Scheme 1). Various substituents such as alkyl, aryl, halide, and CF_3 are tolerated on the phenyl group giving good to moderate yields of the insertion products **2**. The limitations for this transformation are highlighted by the electron rich methoxy-substituted substrate **1j** which gives a low yield of 38%. This procedure was also efficient for $PhMe_2SiH$ and nBu$_3$GeH insertion, delivering silane **2m** and organogermanium **2n** in good yields.

When these reaction conditions were applied to diazo esters **3a** and **3b**, the crude ^{1}H NMR spectra indicated mixtures of stannanes **4** and reduction products **5**, and upon workup, only the latter were isolated (Scheme 2). These examples highlight the instability of α-carbonyl stannanes, which is consistent with previous literature [18].

Table 1
Optimization studies for Sn–H insertion.[a]

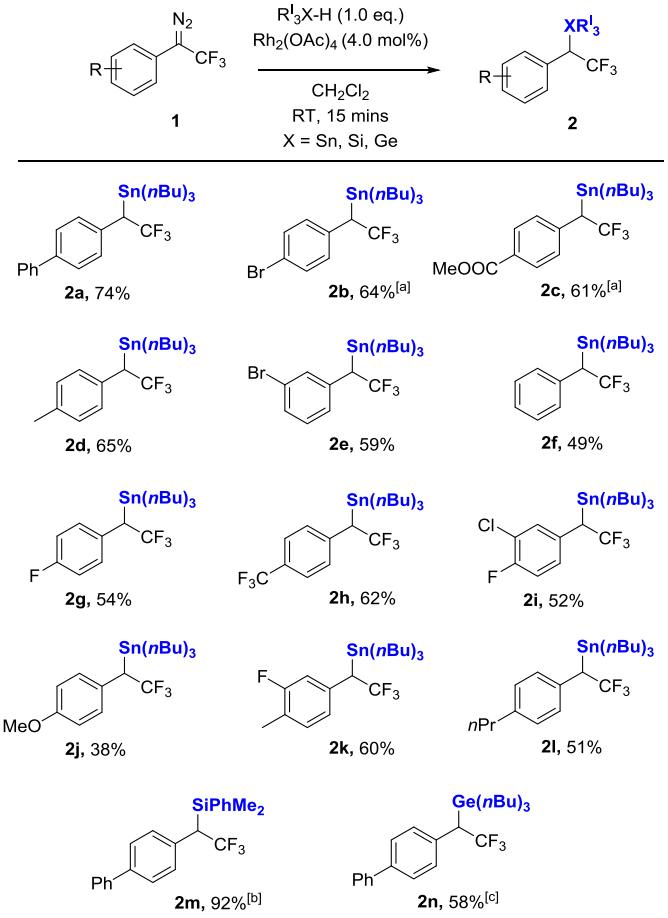


Entry	Catalyst	Solvent	Procedure[c]	Yield[d]
1[b]	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**A**	26
2	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**B**	4
3	$Cu(MeCN)_4PF_4$	CH_2Cl_2	**C**	traces
4	$Rh_2(OAc)_4$	CH_2Cl_2	**A**	25
5	$Rh_2(OAc)_4$	CH_2Cl_2	**C**	64
6	$Cu(OAc)_2$	CH_2Cl_2	**C**	traces
7	$Rh(PPh_3)_3Cl$	CH_2Cl_2	**C**	(6)
8	$Rh_2(OAc)_4$	$CHCl_3$	**C**	(43)
9	$Rh_2(OAc)_4$	Toluene	**C**	(59)
10	$Rh_2(OAc)_4$	Hexane	**C**	(43)
11	$Rh_2(OAc)_4$	DCE	**C**	(45)
12	**$Rh_2(OAc)_4$**	**CH_2Cl_2**	**D**	**74**
13	$Rh_2(OAc)_4$[e]	CH_2Cl_2	**D**	67
14	$Rh_2(OAc)_4$[f]	CH_2Cl_2	**D**	74

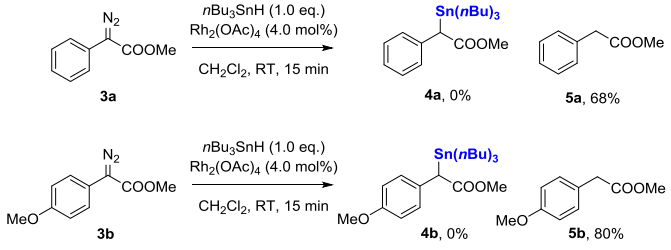
[a] All reactions performed on a 0.1 mmol scale with 1.0 eq. of **1a** and nBu$_3$SnH, with 4.0 mol% catalyst loading, unless stated otherwise.
[b] 2.0 eq. of nBu$_3$SnH.
[c] Procedure A: Syringe pump addition of **1a** solution to a mixture of cat. and nBu$_3$SnH in dichloromethane over 1 h. Procedure B: Syringe pump addition of **1a** and nBu$_3$SnH solution to a catalyst suspension in dichloromethane over 1 h. Procedure C: **1a** and nBu$_3$SnH added to vial and dissolved in dichloromethane (not degassed). The catalyst was then added. Procedure D: **1a** and nBu$_3$SnH added to a vial and dissolved in dichloromethane under anhydrous conditions. In a separate vial was added the catalyst and dichloromethane. The mixture of **1a** and nBu$_3$SnH was added to the catalyst suspension.
[d] All yields are those of isolated products unless stated otherwise. ^{1}H and ^{19}F NMR yields, using ethyl trifluoroacetate as internal reference, are shown in parenthesis.
[e] 2 mol% of catalyst.
[f] 10 mol% of catalyst.

Given that Wang proposed that α-carbonyl stannanes undergo protodestannylation via a putative radical pathway, radical stabilization enthalpies (RSE), which are derived from bond dissociation enthalpies (BDE), may account for the difference in stability of the stannane products. Due to the paucity of experimental tin bond dissociation enthalpies, we performed quantum mechanical calculations in Gaussian 09 rev. D.0.1 [24]. Computation of tin bond dissociation enthalpies is challenging, due to relativistic effects, and lack of experimental data for benchmarking. Grindley and Boyd have benchmarked organotin bond dissociation energies, finding a strong method dependence; we use the B3LYP/SDB-aug-cc-pVTZ//B3LYP/def2-SVPD level of theory described by the latter [25,26]. We also computed the corresponding proto derivatives using the higher G4 method for comparison and confirm good correlation of RSEs (see SI) [27].

Of the compounds calculated, the RSE corresponding to stannane **6b** (5.0 kcal/mol) is lower than the other compounds investigated by at least 10 kcal/mol (Table 2, entry 2). This is consistent with the low propensity for this compound to undergo protodestannylation via a radical pathway. In contrast, the phenyl-substituted ester **6e** has a much higher RSE (20.9 kcal/mol) consistent with the protodestannylation observed experimentally (Table 2, entry 5) [18]. Compound **6c** has significantly lower RSE than the non-fluorinated derivative **6d** with RSEs of 16.4 kcal/mol and 21.8 kcal/mol respectively (Table, entries 3 and 4). This is consistent with reports of the destabilizing effect of trifluoromethyl substitution on carbon-centered radicals [28]. Additionally, we find the RSE corresponding to **6d** and the phenyl substituted ester **6e** to

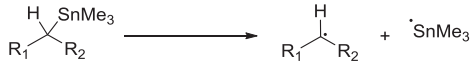


Scheme 1. Rhodium-catalysed insertion into Sn–H bonds with aryl substituted trifluorodiazoethanes. All reactions performed on 0.1 mmol scale following procedure D (Table 1) unless stated otherwise. All yields are those of isolated products. [a] Procedure C. [b] 1.0 eq. of $PhMe_2SiH$ instead of nBu_3SnH. [c] 1.0 eq. of nBu_3GeH instead of nBu_3SnH.



Scheme 2. Reactivity of diazo esters towards nBu_3SnH.

Table 2
Computed bond enthalpies in kcal/mol.[a]



Entry	Stannane	R_1	R_2	BDE	RSE
1	**6a**	H	H	63.6	0.0 (defined)
2	**6b**	H	CO_2Et	58.6	5.0
3	**6c**	C_6H_5	CF_3	47.2	16.4
4	**6d**	C_6H_5	CH_3	41.8	21.8
5	**6e**	C_6H_5	CO_2Me	42.7	20.9

[a] Values computed at the B3LYP/SDB-aug-cc-pVTZ//B3LYP/def2-SVPD level of theory, BDE – bond dissociation enthalpy, RSE – radical stabilization energy.

be similar (RSE = 21.8 kcal/mol and 20.9 kcal/mol respectively).

Despite asymmetric heteroatom-hydrogen insertion reactions with diazo compounds having been extensively studied for many nucleophiles [12], to date there are no examples of catalytic enantioselective Sn–H insertion reactions. This is possibly due to α-diazo carbonyl compounds generating unstable stannane insertion products [18]. Since aryl 2,2,2-trifluorodiazoethanes are converted into stable Sn–H insertion products, we sought to develop an asymmetric protocol.

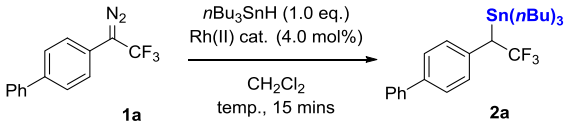
Optimization studies for an asymmetric insertion reaction were performed by testing a range of chiral Rh(II) catalysts (Table 3, entries 1 to 4). For operational simplicity, the chiral catalyst was added to a solution of diazo compound **1a** and tributyltin hydride in dichloromethane in an open vial, a process which allowed for the rapid identification of Rh_2(S-tertPTTL)$_4$ as the most efficient catalyst affording **2a** in 90% ee but low yield (entry 4) [29,30]. When the reaction was performed under inert atmosphere in degassed solvent, a significant improvement of yield was achieved in addition to slight increase of enantioselectivity (entry 5). Decreasing temperature improved ee, however the yield was diminished (entries 6 and 7). At −78 °C, enantioenriched stannane **2a** was isolated in 57% yield and 94% ee.

Comparable results were achieved when electron poor ester **1c** and electron rich 4-methoxy substituted diazo compound **1j** were subjected to the asymmetric insertion protocol, affording stannanes **2c** and **2j** with good to moderate yields with good enantioselectivities. In addition, these optimized reaction conditions were highly efficient for $PhMe_2SiH$ and nBu_3GeH asymmetric insertion, affording silane **2m** and organogermanium **2n** in good and excellent yields respectfully, both with 99% ee (Scheme 3).

3. Conclusion

In summary, we have developed a Rh(II) catalysed trialkyltin hydride insertion reaction into 1-aryl-2,2,2-trifluorodiazoethanes. In contrast to products of Sn–H insertion of α-carbonyl diazo compounds, the α-(trifluoromethyl)benzyl stannanes are bench stable. In addition, the first asymmetric tin hydride insertion with diazo compounds has been disclosed delivering enantioenriched α-(trifluoromethyl)benzyl stannanes. The use of the stannane products in palladium catalysed cross coupling is challenging due to

Table 3
Optimization studies for asymmetric insertion **1a** into nBu_3SnH.[a]

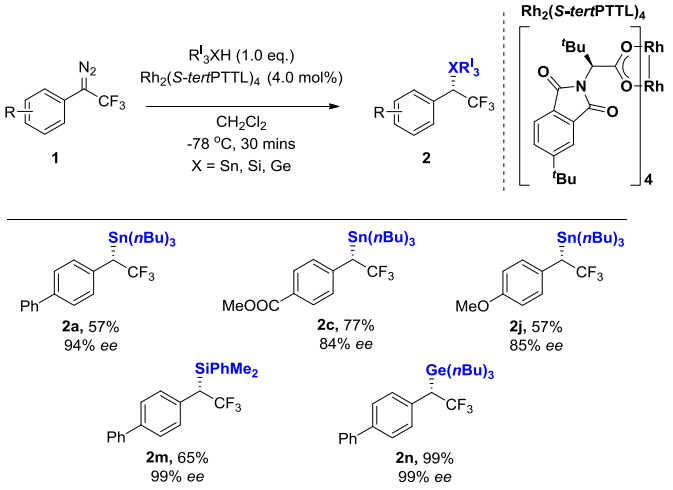


Entry	Procedure	Catalyst	T/°C	Yield 2a/%	*ee*/%
1	A	Rh_2(*S*-DOSP)$_4$	RT	78	7
2	A	Rh_2(*R*-PTAD)$_4$	RT	19	79
3	A	Rh_2(*R*-BTPCP)$_4$	RT	78	−26
4	A	Rh_2(*S*-*tert*PTTL)$_4$	RT	36	−90
5	B	Rh_2(*S*-*tert*PTTL)$_4$	RT	82	−91
6	B	Rh_2(*S*-*tert*PTTL)$_4$	0	74	−92
7[b]	B	Rh_2(*S*-*tert*PTTL)$_4$	−78	57	−94

Yields are those of isolated products.

[a] Procedure A: Diazo and stannane added to vial and dissolved in dichloromethane. To the mixture was added the catalyst. Procedure B: (anhydrous conditions) Diazo and stannane added to a vial and dissolved in dichloromethane. In a separate vial was added the catalyst and more dichloromethane. The diazo/stannane mixture was added to the catalyst suspension.

[b] Reaction time 30 min.



Scheme 3. Asymmetric rhodium-catalysed insertion into X-H bonds (X = Sn, Ge, Si) with trifluorodiazoethanes. Absolute configuration determined by comparison of $[\alpha]^D$ value of **2m** with that reported in the literature [21]. Absolute configuration of other substrates assigned by analogy with **2m**.

their propensity to undergo β-fluoride elimination. However, a recent report has demonstrated that secondary α-(trifluoromethyl) benzyl tosylates can undergo cross coupling without β-fluoride elimination, suggesting that the same might possible for the corresponding stannanes disclosed within [31].

4. Experimental

4.1. General information

All NMR spectra were recorded on Bruker DPX200, AV400 or AV500 spectrometers and are reported as chemical shifts (δ) in parts per million (ppm). ^{1}H and ^{13}C NMR spectra are referenced relative to residual undeuterated solvent peak. ^{19}F NMR spectra are referenced relative to $CFCl_3$. Coupling constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sept (septet), m (multiplet), br (broad). High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using electrospray ionisation (ESI), electron ionisation (EI) or chemical ionisation (CI). Infrared spectra were recorded as neat compound using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. Thin layer chromatographies (TLC) were performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F254. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography columns were performed over Merck silica gel C60 (40 60 μm) using eluent systems as described for each experiment. All solvents and chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fluorochem or Apollo Scientific, and used without further purification, unless stated otherwise.

4.2. Preparation of diazo substrates **1**

All diazo compounds **1** were prepared from the corresponding trifluoroacetophenones, either via general procedure A followed by general procedure B, or in a telescoped process using general procedure C. The trifluoroacetophenones were prepared according to literature procedures [23,32].

4.2.1. General procedure A: preparation of hydrazone diazo precursors **1′**

Procedure from Wang et al. [33] To a round bottom flask equipped with a reflux condenser was added tosylhydrazide (1.0 eq.) and the minimum quantity of solvent (either methanol or toluene according to individual substrates) needed to dissolve the hydrazide at reflux (approximately 1.5 M). Subsequently the reaction was cooled to room temperature and trifluoroacetophenone (1.0 eq.) was added in one portion. The reaction mixture was then stirred at 65 °C (MeOH) or 90 °C (Toluene) over 4–16 h (monitored by TLC). The solution was cooled to room temperature or 0 °C, at which point the product precipitated out of solution (precipitation can be induced by addition of pentane). The precipitate was collected by vacuum filtration and washed with pentane, in which case it was used without further purification. If no precipitation occurred, the solvent was removed under reduced pressure and the residue used in the next step without further purification. Hydrazone derivatives were found to be unstable on silica gel.

4.2.2. General procedure B: preparation of diazo substrates **1**

CAUTION: diazo compounds are presumed to be toxic and potentially explosive and should be handled with care, in a fume hood [34]. Procedure from Xu et al. [35] The Tosyl hydrazone (1.0 eq.) was refluxed in a solution of KOH (2 eq.) in MeOH (0.4 M) for 1 h or until the colour of the solution no longer intensified. The reaction was then cooled to room temperature and diluted with water. The crude product was extracted with CH_2Cl_2 or pentane (see individual substrates for details), washed with saturated solutions of $NaHCO_3$ and brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography.

4.2.3. General procedure C: telescoped preparation of diazo substrates **1**

CAUTION: diazo compounds are presumed to be toxic and potentially explosive and should be handled with care, in a fume hood [34]. To a mixture of tosyl hydrazine (1.0 eq.) in MeOH (1.5 M) was added ketone (1.0 eq). The reaction mixture was heated to reflux for 18 h then allowed to cool to room temperature. Solvent was evaporated under reduced pressure and the residue triturated with pentane, dried under vacuum and used in subsequent steps without additional purification. To the residue was added KOH (2.0 equiv.) in MeOH (0.4 M) and the reaction mixture heated to reflux for 1–2 h, during which the characteristic red colour of diazo compounds appeared. The reaction mixture was allowed to cool to room temperature, poured into water and extracted with pentane (×3). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography.

4.2.4. N′-(1-([1,1′-biphenyl]-4-yl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**1′a**)

Prepared following general procedure A from the corresponding trifluoroacetophenone (6.7 g, 36 mmol), in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (11.4 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.84 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.73 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.60 (m, 2H), 7.50 (m, 2H), 7.43 (m, 1H), 7.35 (m, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.7, 141.6 (q, $^2J_{CF}$ = 35.7 Hz), 139.7, 134.7, 130.1, 129.3, 128.9, 128.8, 128.6, 128.2, 127.4, 124.0, 120.2 (q, $^1J_{CF}$ = 271 Hz), 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.1 (s, 3F). Data consistent with literature values [23].

*4.2.5. 4-(1-Diazo-2,2,2-trifluoroethyl)-1,1′-biphenyl (**1a**)*

Prepared following general procedure B from tosylhydrazone **1'a** (7.41 g, 17.1 mmol). Purified by silica gel chromatography (pentane) and obtained as an orange/red solid (1.86 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.29 (m, 2H), 7.23 (m, 2H), 7.14 (m, 1H), 6.81 (d, $^{3}J_{HH} = 8.1$ Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.2, 128.0, 127.9, 127.7, 127.6, 126.3 (q, $^{1}J_{CF} = 270$ Hz), 125.6, 123.2, 122.1 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.4 (s, 3F). Data consistent with literature values [36].

*4.2.6. N′-(1-(4-bromophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**1'b**)*

Prepared following general procedure A from 4′-bromo-2,2,2-trifluoroacetophenone (2.43 g, 9.6 mmol) in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (3.72 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H) 7.81 (m, 2H), 7.60 (m, 2H), 7.36 (d, $^{3}J_{HH} = 7.8$ Hz, 2H), 7.15 (d, $^{3}J_{HH} = 7.8$ Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.5 (q, $^{2}J_{CF} = 36.0$ Hz), 134.5, 133.7, 130.1, 130.0, 128.4, 126.8, 124.3, 120.0 (q, $^{1}J_{CF} = 273$ Hz), 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.2 (s, 3F). Data consistent with literature values [33].

*4.2.7. 1-Bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (**1b**)*

Prepared following general procedure B from tosylhydrazone **1'b** (3.5 g, 8.3 mmol). Purified by silica gel chromatography (pentane) and obtained as a deep-red liquid (1.21 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 6.97 (d, $^{3}J_{HH} = 8.6$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 125.7 (q, $^{1}J_{CF} = 270$ Hz), 123.8, 122.9, 119.7 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F). Data consistent with literature values [23].

*4.2.8. Methyl-4-(2,2,2-trifluoro-1-(2-tosylhydrazineylidene)ethyl) benzoate (**1'c**)*

Prepared following general procedure A from corresponding trifluoroacetophenone (3.0 g, 12.9 mmol) in toluene (90 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (4.36 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96, (s, 1H), 7.84 (m, 2H), 7.35 (m, 4H), 7.15 (d, 2H), 2.49 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 145.0, 140.4 (q, $^{2}J_{CF} = 36.5$ Hz), 134.5, 133.2, 131.2, 130.0, 129.7, 128.6, 128.2, 120.0 (q, $^{1}J_{CF} = 273.0$ Hz), 53.0, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.1 (s, 3F). Data consistent with literature values [23].

*4.2.9. Methyl 4-(1-diazo-2,2,2-trifluoroethyl)benzoate (**1c**)*

Prepared following a modification of general procedure B: To a solution of tosylhydrazone **1'c** (1.12 g, 2.8 mmol) in MeOH (10 mL) was added NaOMe (303 mg, 5.6 mmol, 2 eq.). A condenser was attached, and the reaction mixture refluxed for 1 h. The reaction was cooled to room temperature and diluted with water. The crude product was extracted with CH_2Cl_2, washed with saturated solutions of $NaHCO_3$ and brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography (pentane/CH_2Cl_2 90:10) and obtained as an orange solid (414 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $^{3}J_{HH} = 8.8$ Hz, 2H), 6.73 (d, $^{3}J_{HH} = 8.8$ Hz, 2H), 3.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4, 126.3, 125.2 (q, $^{1}J_{CF} = 269.0$ Hz), 124.1, 123.3, 122.5, 119.2 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F). Data consistent with literature values [23].

*4.2.10. 4-Methyl-N′-(2,2,2-trifluoro-1-(p-tolyl)ethylidene) benzenesulfonohydrazide (**1'd**)*

Prepared following general procedure A from 2,2,2-trifluoro-1-(*p*-tolyl)ethan-1-one (1.0 g, 5.31 mmol) in methanol (65 °C, 18 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (0.73 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H) 7.81 (d, $^{3}J_{HH} = 8.3$ Hz, 2H), 7.32 (m, 4H), 7.13 (d, $^{3}J_{HH} = 8.3$ Hz, 2H), 2.42 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 142.1, 141.8 (q, $^{2}J_{CF} = 35.8$ Hz), 134.6, 130.7, 129.9, 128.0, 122.1, 119.0 (q, $^{1}J_{CF} = 275$ Hz), 21.7, 21.5 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.4 (s, 3F). Data consistent with literature values [33].

*4.2.11. 1-(1-Diazo-2,2,2-trifluoroethyl)-4-methylbenzene (**1d**)*

Prepared following general procedure B from tosylhydrazone **1'd** (0.72 g, 2.0 mmol), purified by silica gel chromatography (pentane) and obtained as a red liquid (169 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, $^{3}J_{HH} = 8.1$ Hz, 2H), 6.75 (d, $^{3}J_{HH} = 8.1$ Hz, 2H), 1.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 130.7, 126.9 (q, $^{1}J_{CF} = 270$ Hz), 123.1, 120.6, 60.2 (q, $^{2}J_{CF} = 43.9$ Hz), 21.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.5 (s, 3F). Data consistent with literature values [23].

*4.2.12. 1-Bromo-3-(1-diazo-2,2,2-trifluoroethyl)benzene (**1e**)*

Prepared following general procedure C from 3′-bromo-2,2,2-trifluoroacetophenone (2.0 g, 7.9 mmol). Purified by silica gel column chromatography (pentane) and obtained as a red oil (120 mg, 6% over two steps). ^{1}H NMR (500 MHz, C_6D_6): 7.02−6.88 (m, 2H), 6.55 (t, $J = 7.9$ Hz, 1H), 6.52−6.45 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 130.6, 128.7, 125.8, 125.5 (q, $^{1}J_{CF} = 269.3$ Hz), 124.7, 123.5, 120.4, (C=N_2 not observed). ^{19}F NMR (471 MHz, C_6D_6) δ −57.5 (s, 3F). IR (neat) υ/cm^{-1}: 3071, 2082, 1594, 1561, 1481, 1349, 1324, 1261, 1172, 1106, 993, 968, 860, 773, 760, 710, 700, 678 [39].

*4.2.13. 4-Methyl-N′-(2,2,2-trifluoro-1-phenylethylidene) benzenesulfonohydrazide (**1'f**)*

Prepared following general procedure A from trifluoroacetophenone (2.09 g, 12 mmol), in methanol (65 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as an off-white solid (2.79 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H) 7.81 (m, 2H), 7.50 (m, 3H), 7.35 (d, $^{3}J_{HH} = 8.0$ Hz, 2H), 7.25 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 141.4 (q, $^{2}J_{CF} = 35.7$ Hz), 134.6, 130.1, 130.1, 128.3, 128.1, 125.3, 120.1 (q, $^{1}J_{CF} = 273$ Hz), 21.8 (unable to see C=N_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.2 (s, 3F). Data consistent literature values [22].

*4.2.14. (1-Diazo-2,2,2-trifluoroethyl)benzene (**1f**)*

Prepared following general procedure B from tosylhydrazone **1'f** (2.91 g, 8.5 mmol). Purified by silica gel chromatography (pentane) and obtained as a volatile red liquid (544 mg, 35%). ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (m, 2H), 7.21 (m, 1H), 7.12 (d, $^{3}J_{HH} = 8.2$ Hz, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 130.0, 126.7 (q, $^{1}J_{CF} = 269$ Hz), 126.5, 123.9, 122.9 (C=N_2 not observed). ^{19}F NMR (376 MHz, C_6D_6) δ - 57.3 (s, 3F). Data consistent with literature values [22].

*4.2.15. 4-Methyl-N′-(2,2,2-trifluoro-1-(4-fluorophenyl)ethylidene) benzenesulfonohydrazide (**1'g**)*

Prepared following general procedure A from 2,2,2,4′-tetrafluoroacetophenone (1.0 g, 5.20 mmol) in methanol (65 °C, 12 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (1.45 g, 77%). Used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.80 (d, $J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.29-7.19 (m, 4H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2 (d, $^{1}J_{CF} = 252.7$ Hz), 145.2, 134.5, 130.9, 130.8, 130.0, 128.2, 120.1 (q, $^{1}J_{CF} = 274.9$ Hz), 117.7, 117.5, 21.8. ^{19}F NMR (377 MHz, $CDCl_3$):

δ −68.4 (s, 3F), −106.6 (m, 1F). Data consistent with literature values [33].

4.2.16. 1-(1-Diazo-2,2,2-trifluoroethyl)-4-fluorobenzene (**1g**)

Prepared following general procedure B from tosylhydrazone **1'g** (1.45 g, 4.0 mmol). Purified by silica gel chromatography (pentane) and obtained as an orange/red liquid (250 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7 (d, $^{1}J_{CF}$ = 246.8 Hz), 126.0 (q, $^{1}J_{CF}$ = 269.2 Hz), 124.4 (dq, J = 8.1, 1.4 Hz), 119.4 (d, J = 3.5 Hz), 116.8 (d, J = 22.3 Hz), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.6 (s, 3F), −115.9 (s, 1F). IR (neat) υ/cm^{-1}: 3054, 2080, 1512, 1334, 1306, 1270, 1240, 1167, 1099, 957, 825, 735, 609. HRMS (ESI, negative) calculated for $C_8H_3F_4N_2$- ([M − H]-): 203.0238, observed: 203.0233.

4.2.17. 1-(1-Diazo-2,2,2-trifluoroethyl)-4-(trifluoromethyl)benzene (**1h**)

Prepared following general procedure C from 4′-trifluoromethyl-2,2,2-trifluoroacetophenone (1.01 g, 4.2 mmol). Purified by silica gel column chromatography (pentane) and obtained as a yellow oil (46 mg, 4% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73−7.50 (m, 2H), 7.22−7.07 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.3, 128.0 (q, $^{2}J_{CF}$ = 32.9 Hz), 126.5 (q, J = 3.9 Hz), 125.2 (q, $^{1}J_{CF}$ = 269.7 Hz), 124.0 (q, $^{1}J_{CF}$ = 271.8 Hz), 122.0 (d, J = 1.0 Hz), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.4 (s, 3F), −62.6 (s, 3F). IR (neat) υ/cm^{-1}: 2931, 2859, 2088, 1619, 1523, 1325, 1280, 1206, 1169, 1110, 1069, 1016, 958, 831, 738 [39].

4.2.18. 2-Chloro-4-(1-diazo-2,2,2-trifluoroethyl)-1-fluorobenzene (**1i**)

Prepared following general procedure C from the corresponding trifluoroacetophenone (1.0 g, 4.4 mmol). Purified by silica gel column chromatography (pentane) and obtained as a red oil (14 mg, 2% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, J = 8.6 Hz, 1H), 7.13 (dd, J = 6.4, 2.4 Hz, 1H), 6.98-6.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6 (d, $^{1}J_{CF}$ = 249.8 Hz), 126.7, 125.6 (q, $^{1}J_{CF}$ = 269.4 Hz), 124.6 (d, J = 1.3 Hz), 122.3 (m), 121.1 (d, J = 4.2 Hz), 117.9 (d, J = 22.0 Hz), (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.5 (s, 3F), −118.1 (td, J = 7.2, 4.2 Hz, 1F). IR (neat) υ/cm^{-1}: 2925, 2853, 2237, 2172, 2089, 2011, 1599, 1504, 1466, 1324, 1257, 1194, 1145, 1066, 814, 704, 628, 617 [39].

4.2.19. 4-Methyl-N′-(2,2,2-trifluoro-1-(4-methoxyphenyl) ethylidene)benzenesulfonohydrazide (**1'j**)

Prepared following general procedure A from 4′-methoxy-2,2,2-trifluoroacetophenone (4.08 g, 20 mmol) in methanol (65 °C, 12 h). Purified by precipitation upon cooling to room temperature and subsequent filtration. Obtained as a pale-yellow solid (2.31 g, 28%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.80-7.79 (m, 2H), 7.43 (m, 2H), 7.32-7.30 (m, 2H), 7.09-7.06 (m, 2H), 3.87 (s, 3H), 2.45 (s, 3H), (unable to see N−H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 144.1, 141.0 (q, $^{2}J_{CF}$ = 38.9 Hz), 135.3, 129.8, 129.2, 127.7, 120.4 (q, $^{1}J_{CF}$ = 274 Hz), 118.9, 114.2, 54.2, 20.0. ^{19}F NMR (376 MHz, CD_3OD) δ −65.5 (s, 3F). Data consistent with literature values [23].

4.2.20. 1-(1-Diazo-2,2,2-trifluoroethyl)-4-methoxybenzene (**1j**)

Prepared following general procedure B from tosylhydrazone **1'j** (2.0 g, 5.38 mmol). Purified by basic alumina gel chromatography (hexane) and obtained as a red solid (139 mg, 12%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.75-6.73 (m, 2H), 6.60 (d, $^{3}J_{HH}$ = 9.0 Hz, 2H), 3.21 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F). Data consistent with literature values [37].

4.2.21. 4-(1-Diazo-2,2,2-trifluoroethyl)-2-fluoro-1-methylbenzene (**1k**)

Prepared following general procedure C from the corresponding trifluoroacetophenone (1.8 g, 8.7 mmol). Purified by silica gel column chromatography (pentane) and obtained as a red oil (47 mg, 2% over two steps). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.24 (t, J = 8.2 Hz, 1H), 6.86−6.71 (m, 2H), 2.26 (d, $^{4}J_{HF}$ = 1.9 Hz, 3H). ^{13}C NMR (126 MHz, Methylene Chloride-d2) δ 162.4 (d, J = 244.9 Hz), 133.1 (d, J = 6.1 Hz), 126.2 (q, J = 269.0 Hz), 123.4 (d, J = 9.1 Hz), 123.2 (d, J = 17.3 Hz), 118.3 (d, J = 3.3 Hz), 109.6 (d, J = 26.2 Hz), 14.4 (C=N_2 not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.0 (s, 3F), −114.3 (m, 1F). IR (neat) υ/cm^{-1}: 2960, 2933, 2867, 2082, 1629, 1579, 1514, 1354, 1327, 1295, 1273, 1235, 1204, 1104, 1009, 875, 862, 807, 760, 734, 644. Compound **1k** was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

4.2.22. 4-Methyl-N′-(2,2,2-trifluoro-1-(4-propylphenyl)ethylidene) benzenesulfonohydrazide (**1'l**)

Prepared following general procedure A from 4′-N-propyl-2,2,2-trifluoroacetophenone (1.0 g, 4.60 mmol) in methanol (65 °C, 12 h). Purified by cooling to room temperature and subsequent filtration and washing with pentane. Obtained as a white solid (1.33 g, 75%). Used without further purification. ^{1}H NMR (400 MHz, CDCl3): δ 7.98 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.36 7.31 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 2.63 (t, $^{3}J_{HH}$ = 7.7 Hz, 2H), 2.46 (s, 3H), 1.71, 1.62 (m, 2H), 0.97 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.9, 145.0, 142.0 (q, $^{2}J_{CF}$ = 35.6 Hz), 134.7, 130.2, 130.0, 128.1, 122.5, 120.1 (q, $^{1}J_{CF}$ = 274.9 Hz), 77.2, 38.1, 24.3, 21.8, 14.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −68.3 (s, 3F). MP 108−109 °C. IR (neat) υ/cm^{-1}: 3171, 2964, 2924, 2857, 1359, 1170, 1119, 1070, 999, 811, 684. HRMS (ESI, positive) calculated for $C_{18}H_{20}F_3N_2O_2S^+$ ([M+H]$^+$): 385.1192, observed: 385.1202.

4.2.23. 1-(1-Diazo-2,2,2-trifluoroethyl)-4-propylbenzene (**1l**)

Prepared following general procedure B from tosylhydrazone **1'l** (1.33 g, 3.46 mmol), purified by silica gel chromatography (pentane) and obtained as an orange/red liquid (194 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 7.03 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H), 2.60 (t, $^{3}J_{HH}$ = 7.6 Hz, 2H), 1.70-1.61 (m, 2H), 0.96 (t, 3JHH = 7.3 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ −57.4 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 129.7, 125.7 (q, $^{1}J_{CF}$ = 268.6 Hz), 122.5, 120.5, 37.6, 24.6, 13.9, (C=N_2 not observed). IR (neat) υ/cm^{-1}: 2963, 2934, 2874, 2079, 1516, 1345, 1276, 1167, 1145, 1105, 957, 835, 799, 738, 640. HRMS (ESI, negative) calculated for $C_{11}H_{10}F_3N_2^-$ ([M − H]-): 227.0802, observed: 227.0556.

4.3. Diazo insertion reaction

4.3.1. General procedure D: $CF_3C(Ar)N_2$ insertion into nBu_3SnH under inert atmosphere

A flame dried, argon purged vial was charged with aryl 2,2,2-trifluorodiazoethane **1** (1.0 eq., 0.1 mmol), $n$$Bu_3SnH$ (26.5 μL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added $Rh_2(OAc)_4$ (1.8 mg, 4 mol%, 0.004 mmol) and degassed CH_2Cl_2 (0.5 mL). Diazo compound and $n$$Bu_3SnH$ solution were added to the $Rh_2(OAc)_4$ suspension over <1 min at room temperature. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 15 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product purified by silica gel column chromatography.

4.3.2. General procedure E: $CF_3C(Ar)N_2$ insertion into nBu_3SnH in an open vial

To a solution of aryl 2,2,2-trifluorodiazoethane **1** (1.0 eq, 0.1 mmol) and nBu$_3$SnH (26.5 μL, 1.0 eq, 0.1 mmol) in CH_2Cl_2 (1.2 mL) in an open vial was added $Rh_2(OAc)_4$ (1.77 mg, 4 mol%, 0.004 mmol). After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 15 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product purified by silica gel column chromatography.

4.3.3. General procedure F: asymmetric $CF_3C(Ar)N_2$ insertion into nBu_3SnH

A flame dried, argon purged vial was charged with aryl 2,2,2-trifluorodiazoethane **1** (1.0 eq, 0.1 mmol), nBu$_3$SnH (26.5 μL, 1.0 eq, 0.1 mmol) and degassed CH_2Cl_2 (0.7 mL). In a separate flame dried, argon purged vial was added Rh_2(S-tertPTTL)$_4$ (1.77 mg, 4 mol%, 0.004 mmol) and degassed CH_2Cl_2 (0.5 mL) and the mixture was cooled down to −78 °C. The diazo compound and nBu$_3$SnH solution were added to the Rh_2(S-tertPTTL)$_4$ suspension over <1 min at −78 °C. After evolution of N_2 had stopped and characteristic orange/red colour of diazo compound had disappeared, the reaction progress was monitored by TLC. Typically, the reaction was complete in less than 30 min. The reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2, evaporated under reduced pressure and the crude product was purified by silica gel column chromatography.

*4.3.4. (1-([1,1′-biphenyl]-4-yl)-2,2,2-trifluoroethyl) tributylstannane (**2a**)*

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (39 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 3.23 (q, $^3J_{HF}$ = 13.7 Hz, 1H), 1.47-1.39 (m, 6H), 1.28 (m, 6H), 0.97 (m, 6H), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 138.7, 135.8 (q, J = 3.8 Hz), 129.7 (q, $^1J_{CF}$ = 274.3 Hz), 128.9, 128.3, 127.5, 127.3, 127.0, 38.9 (q, 2JCF = 30.9 Hz), 28.8, 27.4, 13.7, 10.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −55.7 (d, $^3J_{FH}$ = 13.6 Hz, 3F). IR (neat) υ/cm^{-1}: 3031, 2956, 2923, 2872, 2854, 1907, 1729, 1612, 1600, 1519, 1488, 1463, 1416, 1377, 1345, 1306, 1281, 1261, 1238, 1204, 1123, 1101, 1075, 1039, 1008, 960, 912, 878, 848, 823, 764, 740, 727, 695, 668, 614. HRMS (CI) calculated for $C_{14}H_{10}F_2^+$([M-nBu$_3$SnF]$^+$): 216.0751, observed: 216.0753; calculated for $C_{12}H_{27}Sn^+$ ([nBu$_3$Sn]$^+$): 291.1129, observed: 291.1145 [38]. Asymmetric reaction was performed using general procedure F. The product (+)-(**2a**) was obtained in 57% yield with this procedure. 94% ee, HPLC conditions; Chiralpak IA column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, tR = 5.89 min for minor isomer, tR = 6.72 min for major isomer: $[\alpha]^D_{25}$ = +55.7 (c 1.46, MeOH).

*4.3.5. (1-(4-bromophenyl)-2,2,2-trifluoroethyl)tributylstannane (**2b**)*

Prepared following general procedure E. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (34 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 3.12 (q, $^3J_{HF}$ = 13.6 Hz, 1H), 1.45-1.37 (m, 6H), 1.29-1.24 (m, 6H), 0.99-0.90 (m, 6H), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.9, 131.9, 130.7 (q, $^1J_{CF}$ = 275.0 Hz), 129.5, 119.6, 38.7 (q, $^2J_{CF}$ = 31.2 Hz), 28.7, 27.4, 13.7, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −55.9 (d, $^3J_{FH}$ = 13.5 Hz, 3F). IR (neat) υ/cm^{-1}: 2957, 2924, 2872, 2854, 1895, 1731, 1592, 1490, 1463, 1412, 1377, 1350, 1339, 1301, 1264, 1238, 1196, 1127, 1100, 1076, 1039, 1011, 960, 941, 875, 843, 809, 769, 747, 721, 691, 671, 649. HRMS (CI) calculated for $C_{12}H_{27}Sn^+$ ([nBu$_3$Sn]$^+$): 291.1129, observed: 291.1138 [38].

*4.3.6. Methyl 4-(2,2,2-trifluoro-1-(tributylstannyl)ethyl)benzoate (**2c**)*

Prepared following general procedure E. Purified by silica gel column chromatography (100% pentane to pentane/CH_2Cl_2 1:1) and obtained as a colourless oil (31 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 3.90 (s, 3H), 3.25 (q, $^3J_{HF}$ = 13.5 Hz, 1H), 1.45-1.31 (m, 6H), 1.25 (m, 6H), 1.01-0.89 (m, 6H), 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.0, 142.5 (q, J = 4.0 Hz), 130.2, 129.3 (q, $^1J_{CF}$ = 275.0 Hz), 127.5, 127.4, 52.2, 39.7 (q, $^2J_{CF}$ = 31.2 Hz), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.3 (d, $^3J_{FH}$ = 13.2 Hz, 3F). IR (neat) υ/cm^{-1}: 2956, 2925, 2873, 2855, 1724, 1610, 1436, 1348, 1275, 1239, 1184, 1112, 1021, 962, 860, 771, 711. HRMS (CI) calculated for $C_{22}H_{36}F_3O_2Sn^+$ ([M+H]$^+$): 509.1689, observed: 509.1677. Asymmetric reaction was performed using general procedure F. The product (+)-(**2c**) was obtained in 77% yield with this procedure. 84% ee, HPLC conditions; Chiralpak IA column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, tR = 10.50 min for major isomer, tR = 12.13 min for minor isomer: $[\alpha]^D_{25}$ = + 1.0 (c 1.26, MeOH).

*4.3.7. Tributyl(2,2,2-trifluoro-1-(p-tolyl)ethyl)stannane (**2d**)*

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (30 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 3.12 (q, $^3J_{HF}$ = 13.8 Hz, 1H), 2.31 (s, 3H), 1.47-1.32 (m, 6H), 1.26 (m, 6H), 0.99-0.90 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.4, 133.4 (q, J = 3.9 Hz), 129.7 (q, $^1J_{CF}$ = 275.0 Hz), 129.5, 127.9, 38.7 (q, $^2J_{CF}$ = 30.8 Hz), 28.8, 27.4, 21.1, 13.7, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.0 (d, $^3J_{FH}$ = 13.7 Hz, 3F). IR (neat) υ/cm^{-1}: 2957, 2923, 2872, 2855, 1513, 1463, 1342, 1309, 1241, 1199, 1123, 1103, 1074, 1042, 876, 808, 719.43, 665. HRMS (CI) calculated for $C_9H_8F_2^+$([M-nBu$_3$SnF]$^+$): 154.0594, observed: 154.0585; calculated for $C_{12}H_{27}Sn^+$ ([nBu$_3$Sn]$^+$): 291.1129, observed: 291.1129 [38].

*4.3.8. (1-(3-Bromophenyl)-2,2,2-trifluoroethyl)tributylstannane (**2e**)*

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (31 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.29 (m, 2H), 7.15 (t, J = 8.1 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 3.12 (q, $^3J_{HF}$ = 13.5 Hz, 1H), 1.45-1.34 (m, 6H), 1.27 (m, 6H), 1.01-0.90 (m, 6H), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3-139.1 (m), 130.7, 130.3, 129.3 (q, $^1J_{CF}$ = 275.0 Hz), 128.9, 126.3, 122.9, 38.9 (q, $^2J_{CF}$ = 31.2 Hz), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.7 (d, $^3J_{FH}$ = 13.4 Hz, 3F). IR (neat) υ/cm^{-1}: 2957, 2923, 2872, 2854, 1593, 1563, 1475, 1378, 1341, 1239, 1195, 1128, 1088, 1039, 996, 877, 779, 713, 692, 620. HRMS (CI) calculated for $C_{12}H_{27}Sn^+$ ([nBu$_3$Sn]$^+$): 291.1129, observed: 291.1132 [38].

*4.3.9. Tributyl(2,2,2-trifluoro-1-phenylethyl)stannane (**2f**)*

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (22 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 2H), 7.17-7.13 (m, 3H), 3.16 (q, $^3J_{HF}$ = 13.7 Hz, 1H), 1.43-1.36 (m, 6H), 1.26 (m, 6H), 0.97-0.90 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.6 (q, J = 3.9 Hz), 129.7 (q, $^1J_{CF}$ = 274.9 Hz), 128.8, 127.9, 125.8, 39.2 (q, $^2J_{CF}$ = 30.9 Hz), 28.7, 27.4, 13.7, 10.5. ^{19}F NMR (377 MHz, $CDCl_3$): δ −55.8 (d, $^3J_{FH}$ = 13.5 Hz, 3F). IR (neat) υ/cm- [1]: 2957, 2924, 2872, 2854, 1601, 1495, 1456, 1356, 1277, 1240, 1203, 1125,

1074, 1034, 874, 757, 698, 671, 615. HRMS (CI) calculated for $C_8H_6F_2^+$([M-*n*Bu_3SnF]$^+$): 140.0438 observed: 140.0426; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1135 [38].

4.3.10. Tributyl(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)stannane (**2g**)

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (25 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, J = 8.4, 5.4 Hz, 2H), 6.98 (t, J = 8.7 Hz, 2H), 3.13 (q, $^3J_{HF}$ = 13.6 Hz, 1H), 1.46-1.34 (m, 6H), 1.26 (m, 6H), 1.00-0.89 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2 (d, $^1J_{CF}$ = 244.5 Hz), 132.4 (q, J = 3.9 Hz), 129.5 (q, $^1J_{CF}$ = 274.9 Hz), 129.5 (q, J = 7.8 Hz), 115.6 (d, J = 21.3 Hz), 38.3 (q, $^2J_{CF}$ = 31.2 Hz), 28.7, 27.4, 13.7, 10.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ −56.4 (d, $^3J_{FH}$ = 3.6 Hz, 3F), −117.3 (m, 1F). IR (neat) υ/cm^{-1}: 2958, 2924, 2873, 2855, 1607, 1509, 1464, 1420, 1342, 1272, 1246, 1228, 1200, 1161, 1117, 1094, 1042, 961, 876, 825, 791, 721, 664. HRMS (CI) calculated for $C_8H_5F_3^+$([M-*n*Bu_3SnF]$^+$): 158.0343 observed: 158.0330; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1133 [38].

4.3.11. Tributyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) stannane (**2h**)

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (32 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 3.24 (q, $^3J_{HF}$ = 13.4 Hz, 1H), 1.49−1.32 (m, 6H), 1.32−1.16 (m, 6H), 1.02−0.90 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0, 129.1 (q, $^1J_{CF}$ = 271.8 Hz), 127.8 (q, $^2J_{CF}$ = 32.7 Hz), 127.6 (t, J = 1.4 Hz), 125.6 (q, J = 3.5 Hz), 124.2 (q, $^1J_{CF}$ = 271.8 Hz), 39.2 (q, $^2J_{CF}$ = 31.3 Hz), 28.5, 27.2, 13.5, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −55.5 (d, $^3J_{FH}$ = 13.4 Hz, 3F), −62.4 (3F). IR (neat) υ/cm^{-1}: 2959, 2925, 2874, 2856, 1620, 1582, 1519, 1464, 1423, 1378, 1326, 1286, 1240, 1202, 1166, 1121, 1103, 1069, 1019, 960, 909, 879, 849, 825, 767, 742, 690, 671. HRMS (CI) calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1129 [38].

4.3.12. Tributyl(1-(3-chloro-4-fluorophenyl)-2,2,2-trifluoroethyl) stannane (**2i**)

Prepared following general procedure D, on 0.05 mmol scale. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (13 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, J = 6.9, 2.3 Hz, 1H), 7.06 (t, J = 8.7 Hz, 1H), 7.00-6.97 (m, 1H), 3.09 (q, $^3J_{HF}$ = 13.4 Hz, 1H), 1.44-1.38 (m, 6H), 1.30-1.23 (m, 6H), 0.99-0.92 (m, 6H), 0.87 (t, $^1J^{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.5 (d, $^1J_{CF}$ = 247.8 Hz), 134.1-133.8 (m), 129.8, 129.3 (q, $^1J_{CF}$ = 275.0 Hz), 127.5 (d, J = 7.0 Hz), 121.2 (d, J = 17.9 Hz), 116.8 (d, J = 21.0 Hz), 38.2 (q, $^2J_{CF}$ = 31.5 Hz), 28.7, 27.4, 13.7, 10.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ −56.2 (d, $^3J_{FH}$ = 13.2 Hz, 3F), −119.6- (m, 1F). IR (neat) υ/cm^{-1}: 2958, 2924, 2855, 1499, 1236, 1230, 1109. HRMS (CI) calculated for $C_8H_4ClF_3^+$ ([M-*n*Bu_3SnF]$^+$): 191.9954 observed: 191.9974; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1146 [38].

4.3.13. Tributyl(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)stannane (**2j**)

Prepared following general procedure D. Purified by preparative TLC (5% EtOAc in cyclohexane) and obtained as a colourless oil (18.3 mg, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11−7.02 (m, 2H), 6.87−6.79 (m, 2H), 3.79 (s, 3H), 3.09 (q, $^3J_{HF}$ = 13.8 Hz, 1H), 1.49 1.30 (m, 6H), 1.26 (h, J = 7.3 Hz, 6H), 1.02−0.87 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 129.8 (q, $^1J_{CF}$ = 274.9 Hz), 129.3, 128.5 (q, J = 4.2 Hz), 114.2, 55.4, 38.1 (q, $^2J_{CF}$ = 30.9 Hz), 28.8, 27.4, 13.7, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.5 (d, $^3J_{FH}$ = 13.6 Hz, 3F). IR (neat) υ/cm^{-1}: 2956, 2924, 2872, 2854, 1612, 1581, 1511, 1464, 1443, 1423, 1377, 1351, 1307, 1283, 1250, 1235, 1202, 1180, 1122, 1100, 1075, 1038, 961, 931, 875, 849, 821, 775, 747, 726, 687, 665. HRMS (CI) calculated for $C_9H_8F_2O^+$ ([M-*n*Bu_3SnF]$^+$): 170.0543, observed: 170.0520; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1116 [38]. Asymmetric reaction was performed using general procedure F. The product (−)-(**2j**) was obtained in 57% yield with this procedure. 85% ee, HPLC conditions; Chiralpak IC column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, tR = 9.20 min for major isomer, tR = 10.11 min for minor isomer: $[\alpha]^D_{25}$ = −0.6 (c 0.46, MeOH).

4.3.14. Tributyl(2,2,2-trifluoro-1-(3-fluoro-4-methylphenyl)ethyl) stannane (**2k**)

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (14.5 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13−7.02 (m, 1H), 6.88−6.74 (m, 2H), 3.11 (q, $^3J_{HF}$ = 13.6 Hz, 1H), 2.23 (d, J = 1.9 Hz, 3H), 1.50−1.34 (m, 6H), 1.34−1.13 (m, 6H), 1.04−0.89 (m, 6H), 0.86 (t, $^3J_{HH}$ = 7.2 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4 (d, $^1J_{CF}$ = 244.6 Hz), 136.2 (dd, J = 7.8, 3.9 Hz), 131.7 (d, J = 5.8 Hz), 129.5 (q, $^1J_{CF}$ = 274.8 Hz), 123.3 (d, J = 3.1 Hz), 122.1 (d, J = 17.2 Hz), 114.4 (d, J = 23.2 Hz), 39.2−38.2 (m), 28.7, 27.4, 14.3 (d, J = 3.3 Hz), 13.7, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.0 (d, $^3J_{FH}$ = 13.5 Hz, 3F), −117.2 (ddd, J = 10.6, 8.4, 2.2 Hz, 1F). IR (neat) υ/cm^{-1}: 2957, 2925, 2873, 2855, 627, 1579, 1510, 1463, 1425, 1378, 1340, 1290, 1272, 1238, 1207, 1150, 1128, 1075, 1041, 999, 958, 876, 851, 817, 787, 755, 710, 683. HRMS (CI) calculated for $C_9H_7F_3^+$ ([M-*n*Bu_3SnF]$^+$): 172.0500, observed: 173.0472; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1122 [38].

4.3.15. Tributyl(2,2,2-trifluoro-1-(4-propylphenyl)ethyl)stannane (**2l**)

Prepared following general procedure D. Purified by silica gel column chromatography (pentane) and obtained as a colourless oil (25 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 3.13 (q, $^3J_{HF}$ = 13.8 Hz, 1H), 2.55 (t, J = 7.6 Hz, 2H), 1.62 (m, 2H), 1.45-1.31 (m, 6H), 1.25 (m, 6H), 0.98 0.89 (m, 9H), 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.2, 133.6 (q, J = 3.9 Hz), 129.8 (q, $^1J_{CF}$ = 274.8 Hz), 128.8, 127.9, 38.7 (q, $^2J_{CF}$ = 30.7 Hz), 37.7, 28.8, 27.4, 24.6, 13.9, 13.7, 10.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ −56.0 (d, $^3J_{FH}$ = 13.8 Hz, 3F). IR (neat) υ/cm^{-1}: 2958, 2926, 2872, 2855, 1512, 1463, 1343, 1240, 1198, 1125, 1106, 1041, 877, 668. HRMS (CI) calculated for $C_{11}H_{12}F_2^+$ ([M-*n*Bu_3SnF]$^+$): 182.0907, observed: 182.0905; calculated for $C_{12}H_{27}Sn^+$ ([*n*Bu_3Sn]$^+$): 291.1129, observed: 291.1136 [38].

4.3.16. (1-([1,1′-biphenyl]-4-yl)-2,2,2-trifluoroethyl) dimethyl(phenyl)silane (**2m**)

Prepared following general procedure D, with substitution of *n*Bu_3SnH for $PhMe_2SiH$ (15.3 μL, 1.0 eq, 0.1 mmol). Purified by silica gel column chromatography (5−15% CH_2Cl_2 in pentane) and obtained as a white solid in 92% yield (34 mg, 0.09 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.3 Hz, 2H), 7.49-7.41 (m, 4H), 7.40-7.30 (m, 6H), 7.06 (d, J = 8.1 Hz, 2H), 3.16 (q, J = 12.9 Hz, 1H), 0.48 (s, 3H), 0.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 139.5, 135.3, 134.3, 132.9 (q, J = 3.2 Hz), 129.8, 129.5, 128.9, 128.3 (q, J = 277.7 Hz, CF_3), 127.9, 127.4, 127.1, 127.1, 43.8 (q, J = 27.7 Hz), −3.4, −3.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.5 (t, J = 13.0 Hz, 3F). IR (neat) υ/cm^{-1} 3071, 3031, 2963, 2905, 2362, 2284, 1488, 1239, 1151, 1133, 1068, 810, 764, 739, 695, 649. HRMS (EI) calculated for $C_{22}H_{21}F_3Si^+$ (M^+): 370.1359, observed: 370.1363. The asymmetric reaction was performed using general procedure F, with substitution of *n*Bu_3SnH for $PhMe_2SiH$ (15.3 μL, 1.0 eq, 0.1 mmol). Purified by silica gel column chromatography (5−15% CH_2Cl_2 in pentane). The product (+)-(**2m**)

was obtained in 65% and 99% ee, HPLC conditions; Chiralcel OJ-H column, hexane/^{i}PrOH = 99:1, flow rate = 1.0 mL/min, 25 °C, wavelength = 250 nm, tR = 15.06 min for major isomer, tR = 20.53 min for minor isomer: $[\alpha]^{D}_{25} = +75.8$ (c 0.85, MeOH).

4.3.17. (1-([1,1′-biphenyl]-4-yl)-2,2,2-trifluoroethyl) tributylgermane (**2n**)

Prepared following general procedure D, with substitution of *n*Bu$_3$SnH for *n*Bu$_3$GeH (25.8 μL, 1.0 eq, 0.1 mmol). Purified by silica gel column chromatography (pentane) and obtained as a colourless oil in 58% yield (28 mg, 0.06 mmol). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.61-7.58 (m, 2H), 7.56-7.53 (m, 2H), 7.47-7.42 (m, 2H), 7.37-7.33 (m, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 3.15 (q, 3JHF = 13.2 Hz, 1H), 1.34-1.24 (m, 12H), 0.92-0.83 (m, 15H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 140.8, 139.3, 134.3, 129.0, 128.9 (q, $^{1}J_{CF}$ = 276.8 Hz), 128.9, 127.4, 127.3, 127.1, 41.0 (q, $^{2}J_{CF}$ = 28.8 Hz), 27.0, 26.6, 13.8, 12.7. ^{19}F NMR (377 MHz, CDCl$_3$): δ −57.1 (d, $^{3}J_{FH}$ = 13.2 Hz, 3F). IR (neat) υ/cm^{-1}: 3032, 2956, 2927, 2871, 2857, 1910, 1600, 1520, 1488, 1464, 1416, 1378, 1344, 1306, 1281, 1262, 1242, 1205, 1141, 1131, 1109, 1063, 1008, 964, 912, 884, 855, 826, 765, 743, 729, 695, 681, 654, 616. HRMS (CI) calculated for $C_{26}H_{41}F_3GeN^{+}$ ([M + NH$_4$]$^{+}$): 498.2397, observed: 498.2435. The asymmetric reaction was performed using general procedure F, with substitution of *n*Bu$_3$SnH for *n*Bu$_3$GeH (25.8 μL, 1.0 eq, 0.1 mmol). The product (+)-(**2n**) was obtained in 99% yield with this procedure. 99% ee, HPLC conditions; Chiralpak IC column, hexane = 100%, flow rate = 1.0 mL/min, 25 °C, wavelength = 254 nm, tR = 6.15 min for major isomer, tR = 6.97 min for minor isomer: $[\alpha]^{D}_{25} = +54.3$ (c 3.46, MeOH).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2018.11.022.

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